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Docket No. AP35699 - 090495.0282
Attorney: Rochelle K. Seide - Tel. 1 212 408-2626
Page 1 of 97
Filed: February 20, 2004
Express Mail No. ER589232951US

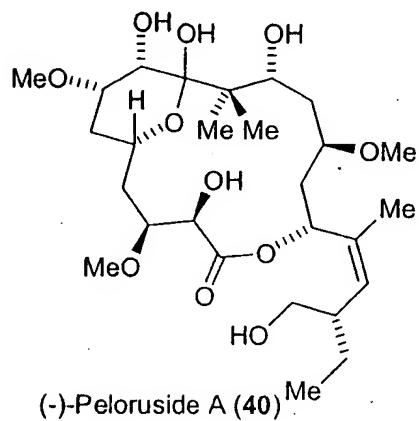


FIG. 1

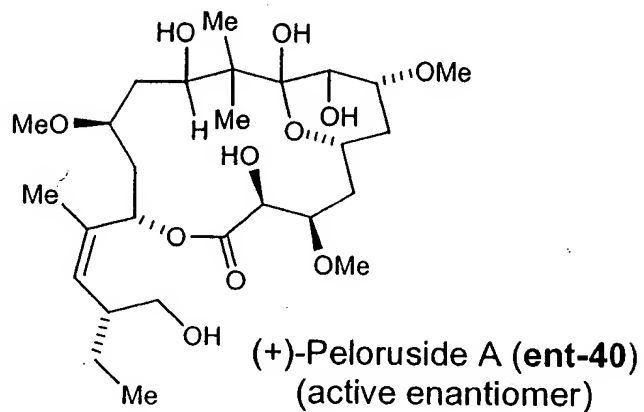


FIG. 2

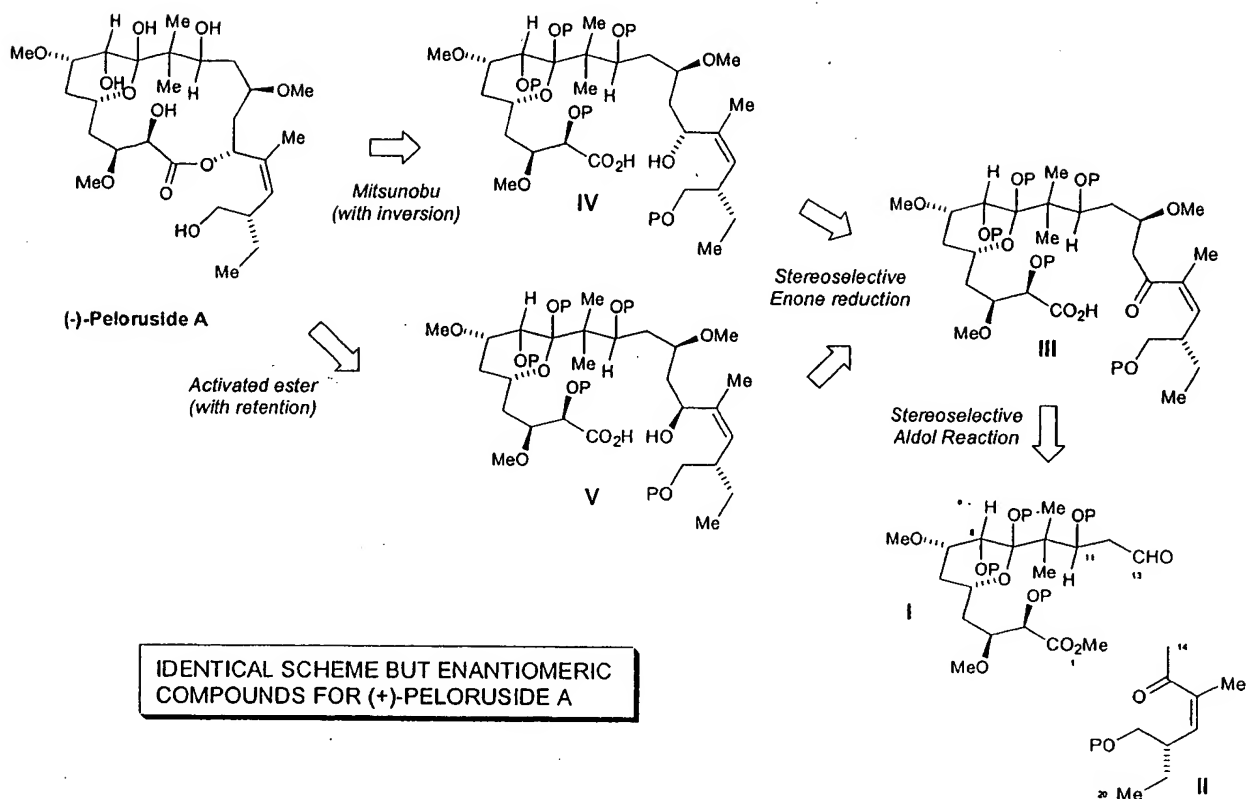
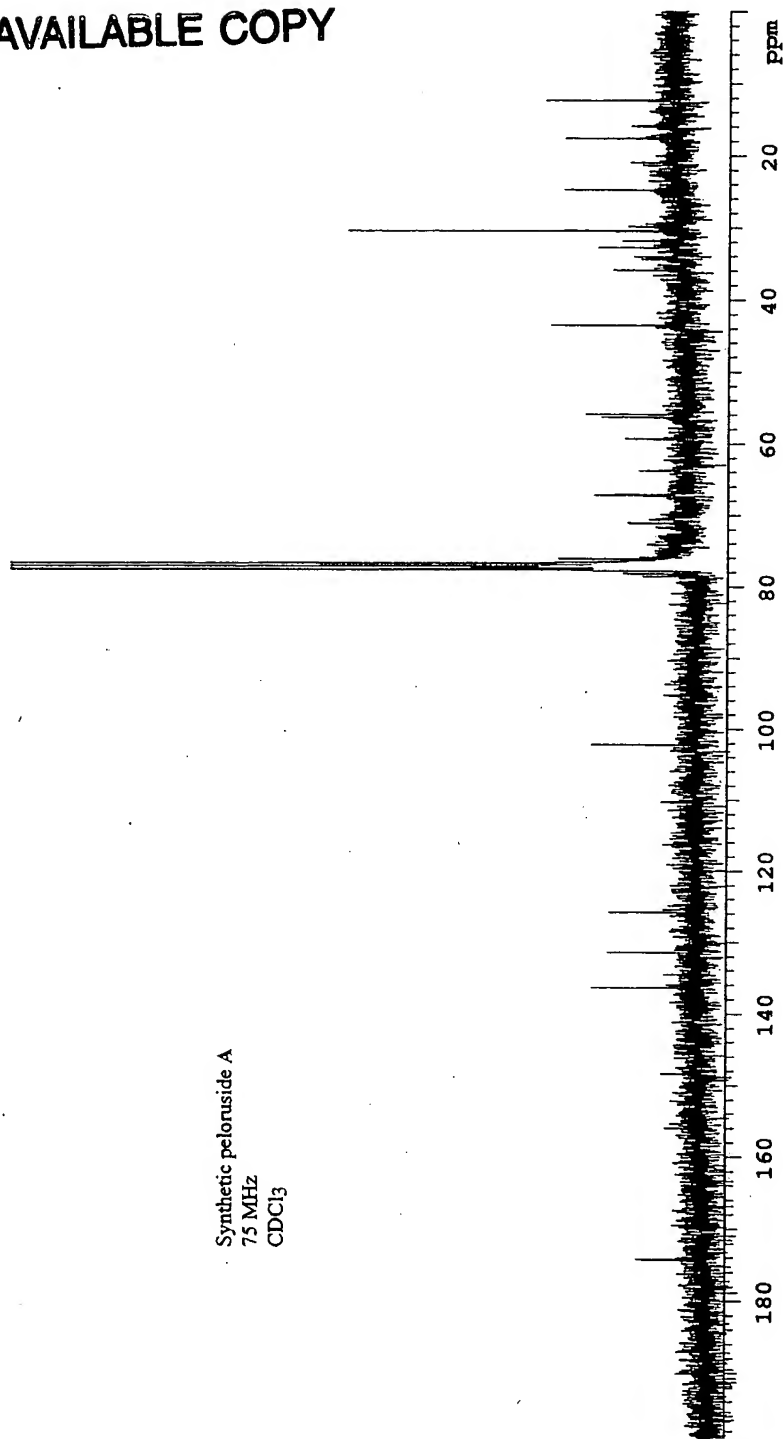


FIG. 3

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Synthetic peloruside A
75 MHz
CDCl₃

FIG. 4

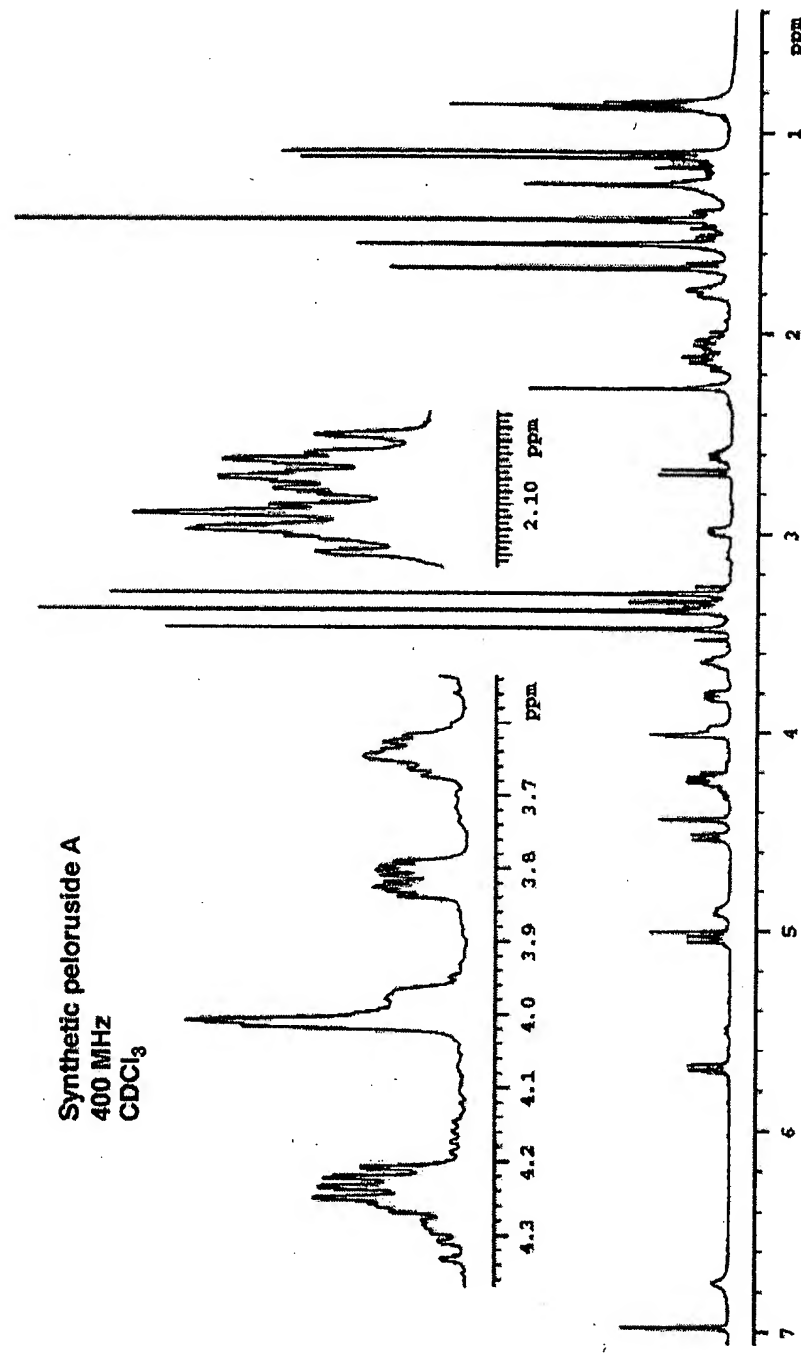


FIG. 5

C1-C13 Fragment:

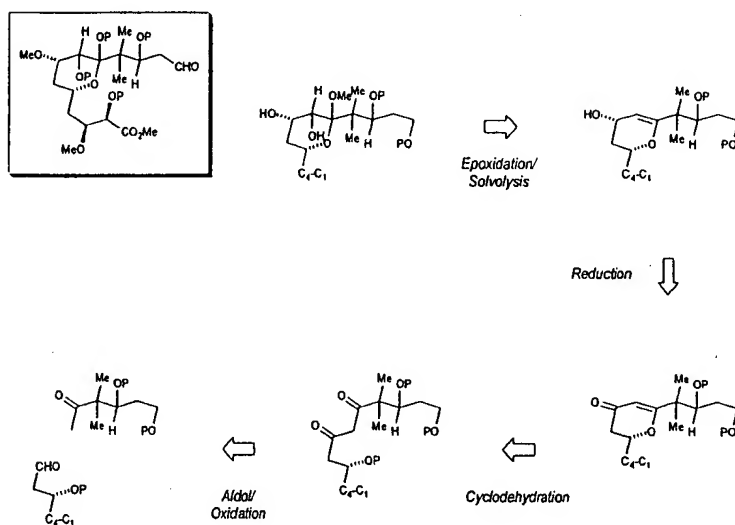


FIG. 6

C1-C13 Fragment: Problematic Glycal-Epoxyde Solvolysis

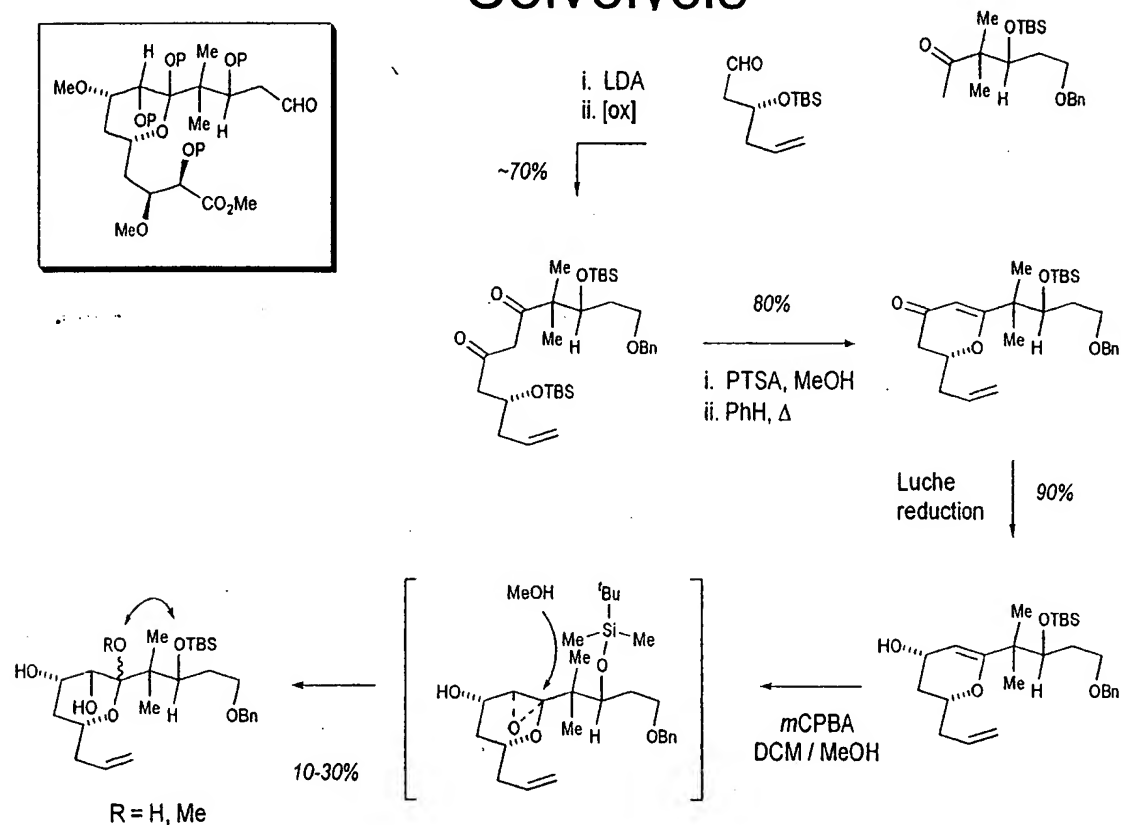


FIG. 7

Solution: Eliminate C11 Stereogenic Centrum

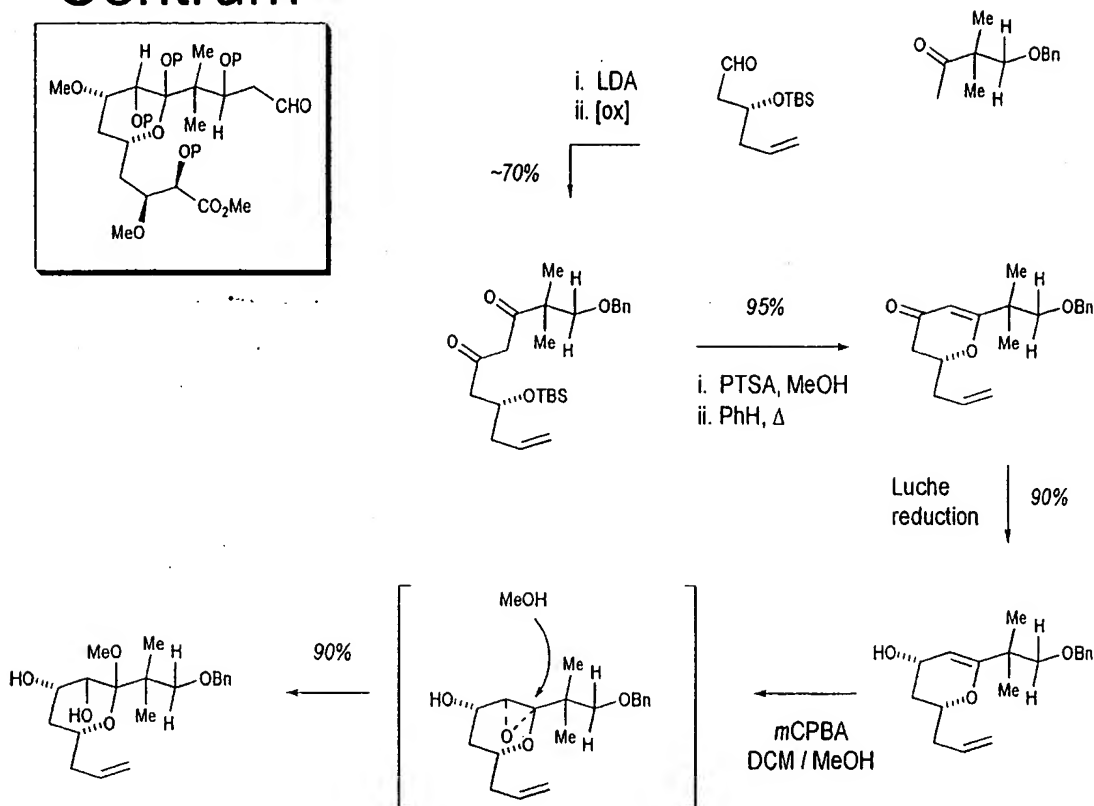


FIG. 8

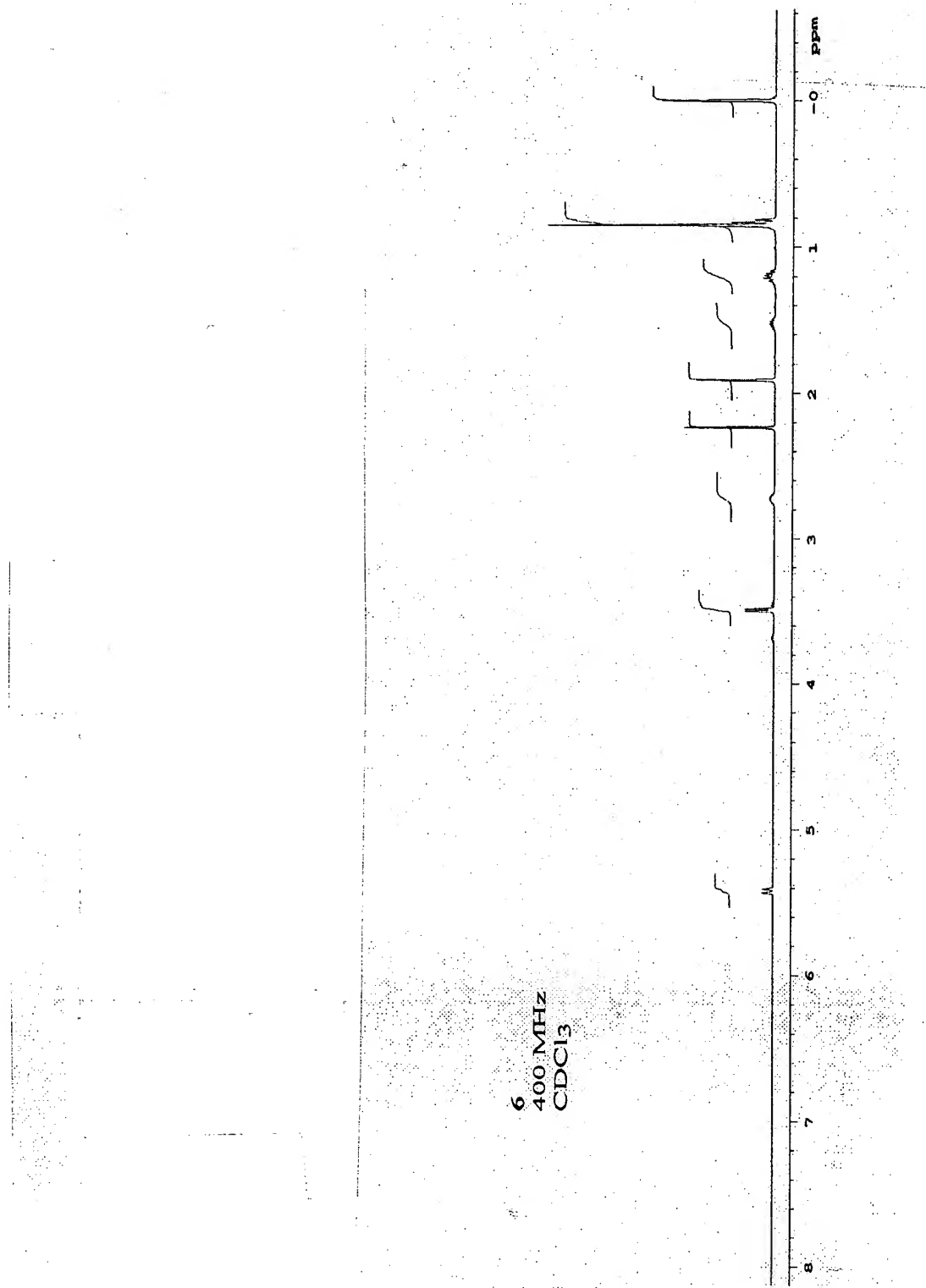


FIG. 9

6
75 MHz
CDCl₃

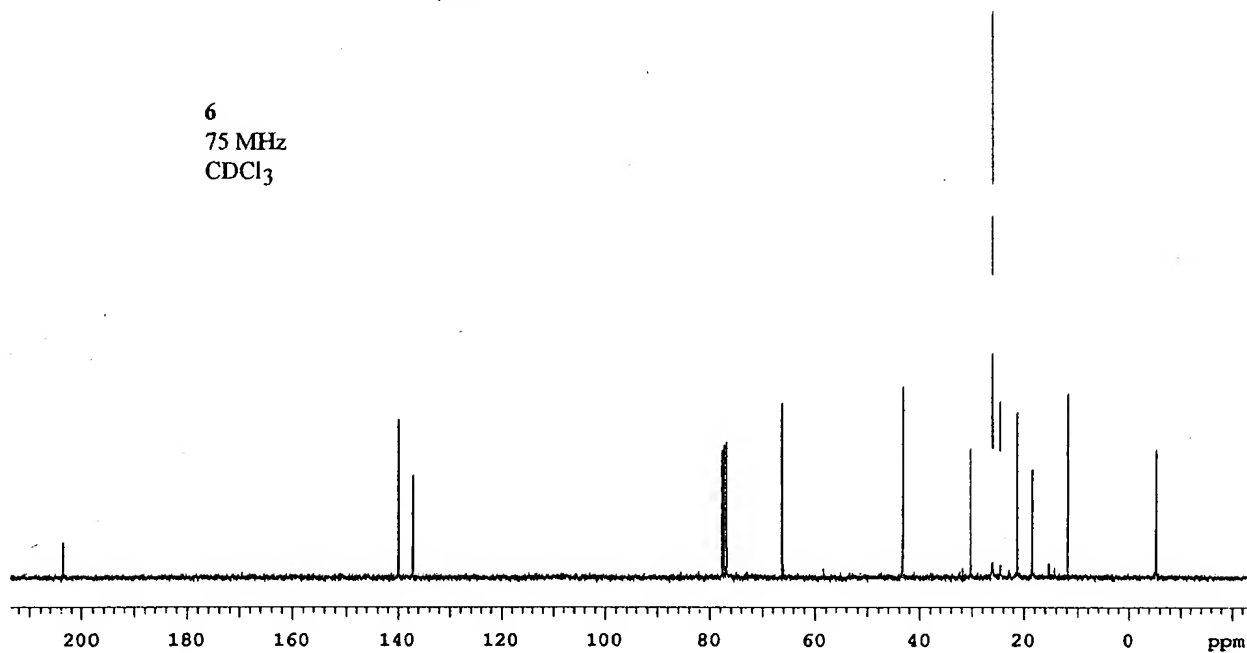


FIG. 10

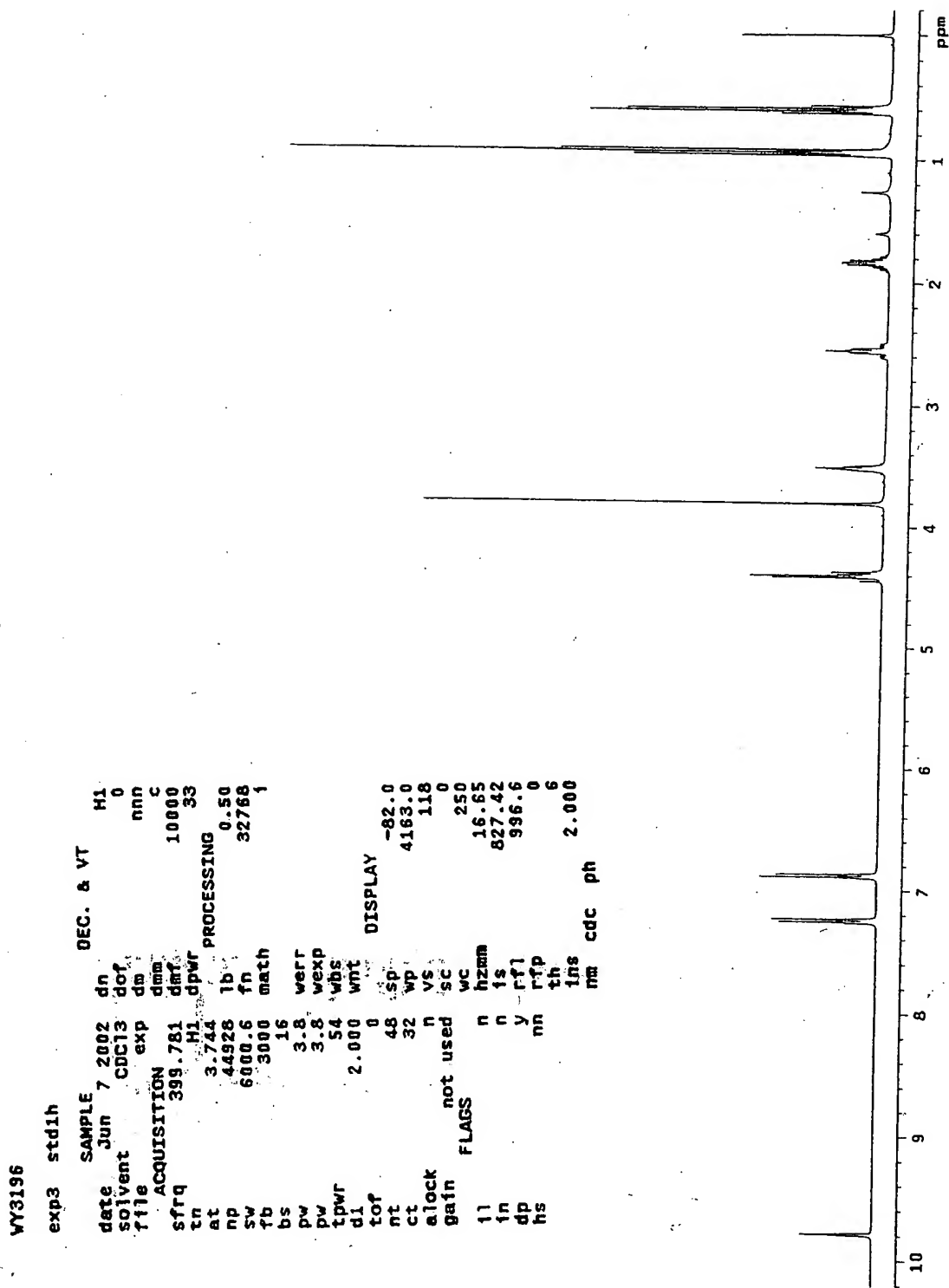


FIG. 11

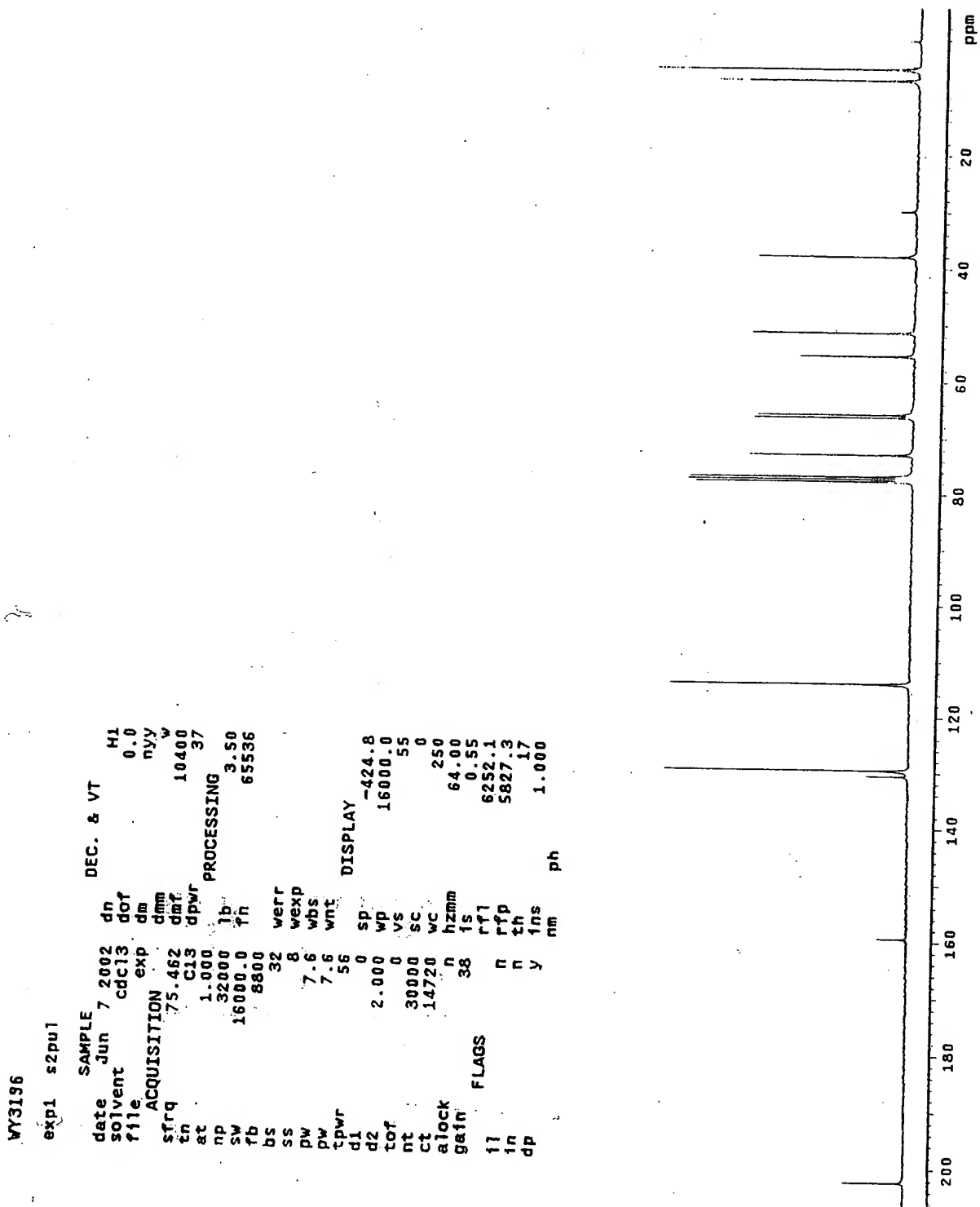


FIG. 12

SAMPLE		date Jun 10 2002		DEC. & VT	
data	solvent	CDC13	exp	dn	0
file	ACQUISITION	399.781	M1	dm	nnn
sfreq	at	3.744	44928	dam	10000
tn	np	6080.6	3000	dmf	33
np	sw	3.8	3.8	dpwr	PROCESSING
fb	bs	54	2.000	lb	0.50
pw	pw	54	2.000	fn	32768
dpwr	di	0	0	math	1
di	tof	48	48	warr	
nt	ct	48	48	wexp	
alock	gain	not used	8	wds	
gain	flags	not used	8	wnt	DISPLAY
fl	in	n	n	sp	-82.0
in	dp	n	y	wp	4163.0
dp	hs	nn	nn	vs	152
hs				sc	0
				wc	250
				h2mm	16.65
				fs	827.42
				rfl	996.6
				rfp	0
				th	6
				ins	2.000
				nm	cdc ph

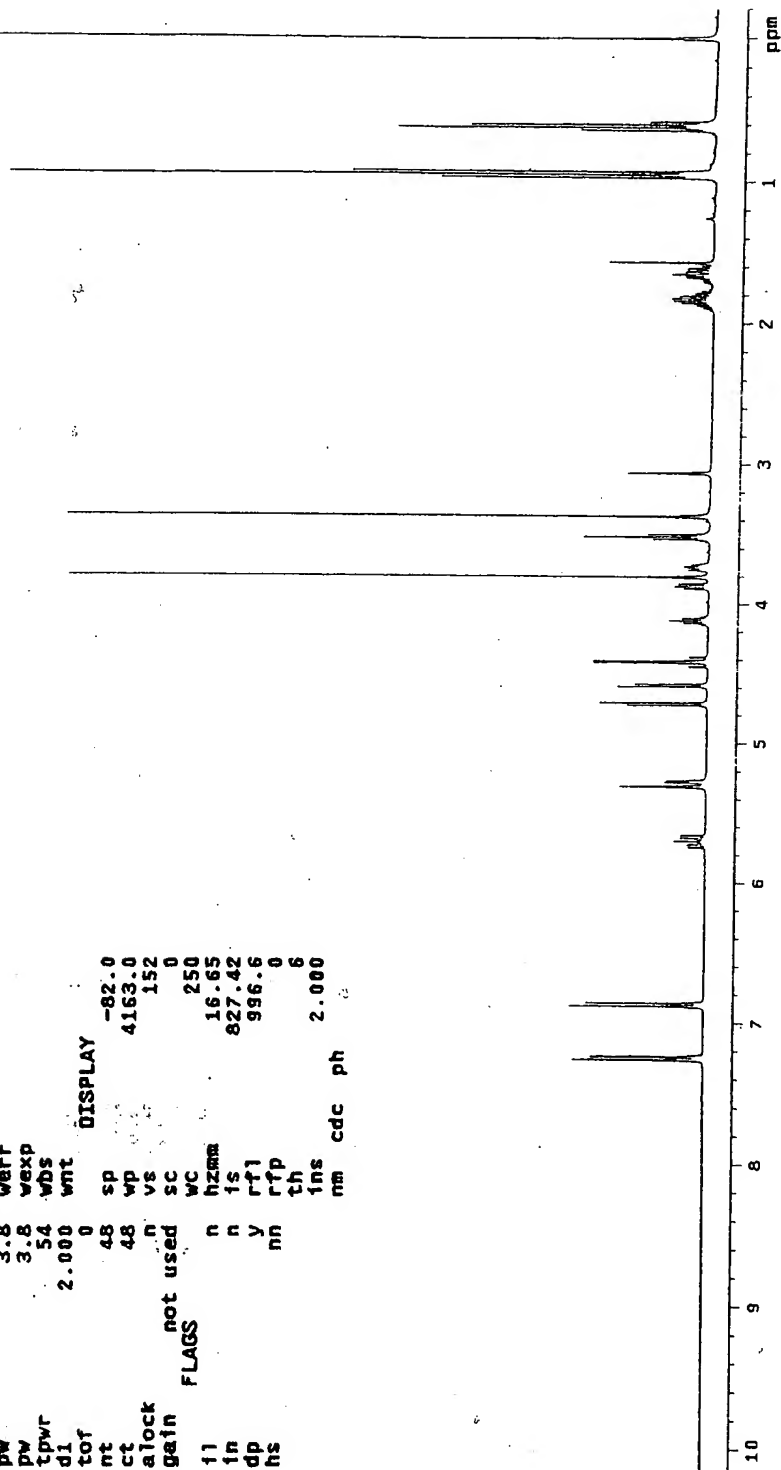
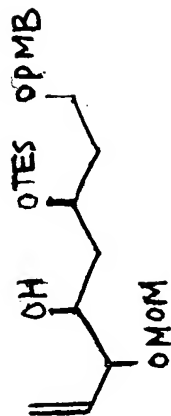


FIG. 13

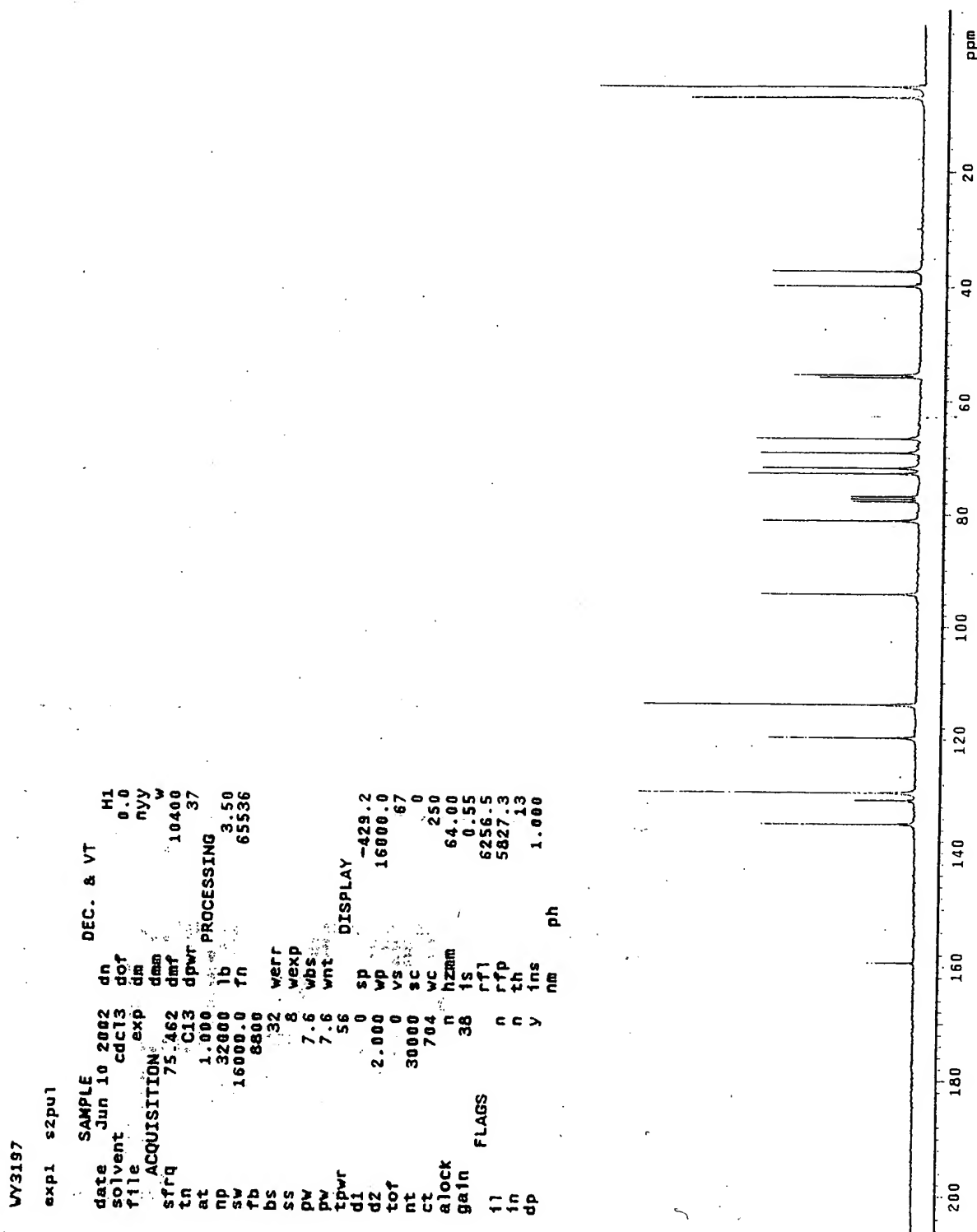


FIG. 14

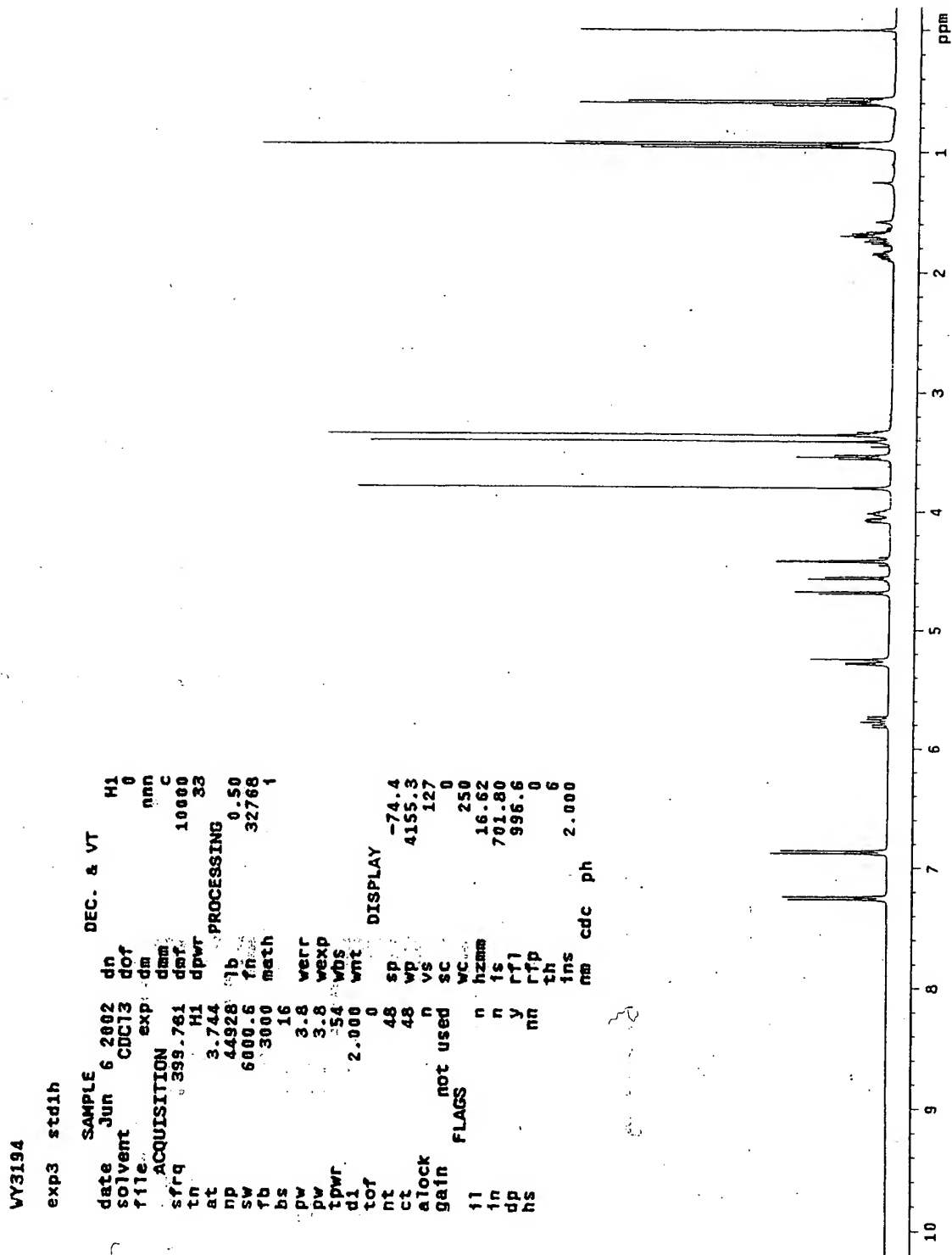


FIG. 15

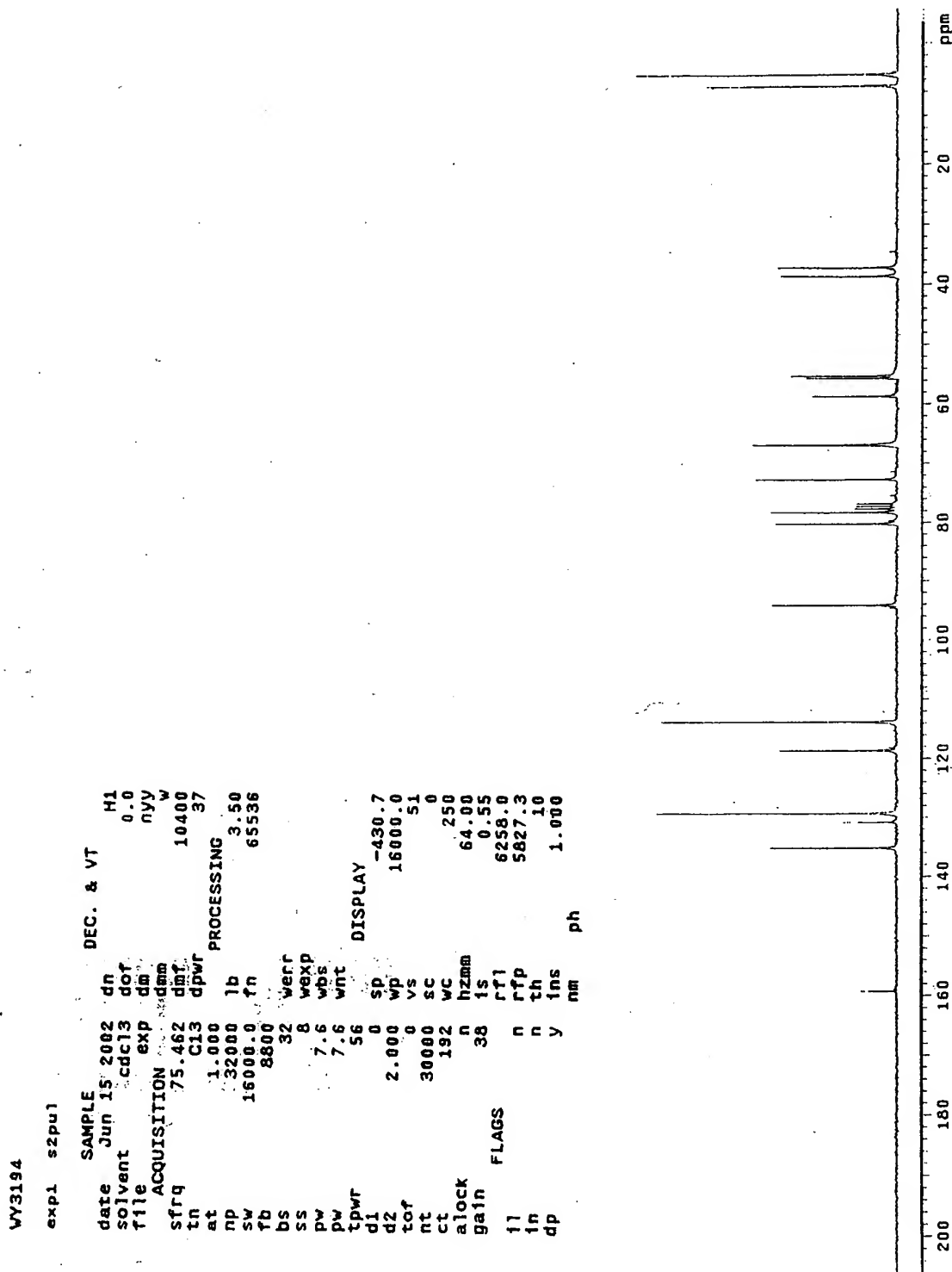


FIG. 16

SAMPLE

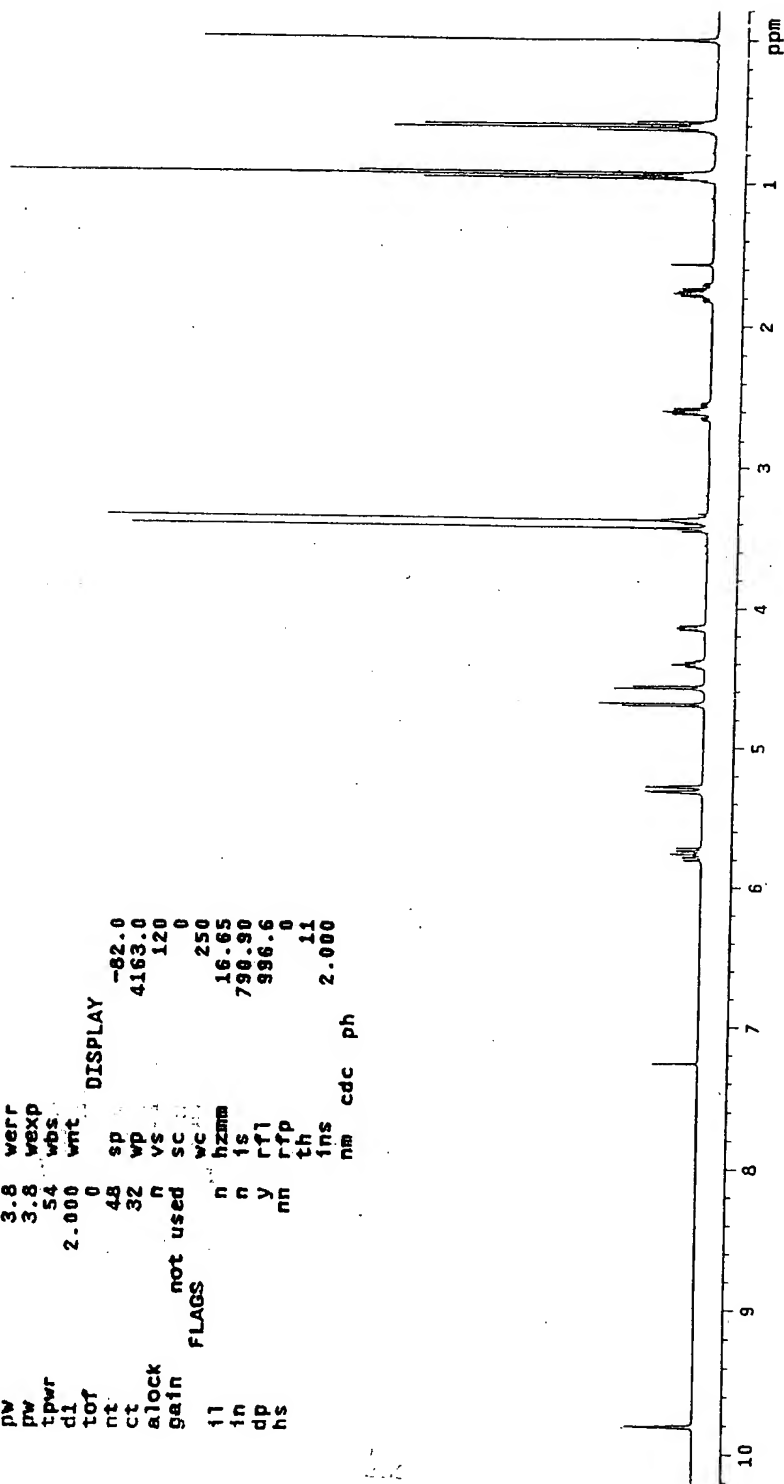
C=C[C@H](OC(=O)C)C[C@H](OC(=O)C)C[C@H](OC(=O)C)C(=O)O

FIG. 17

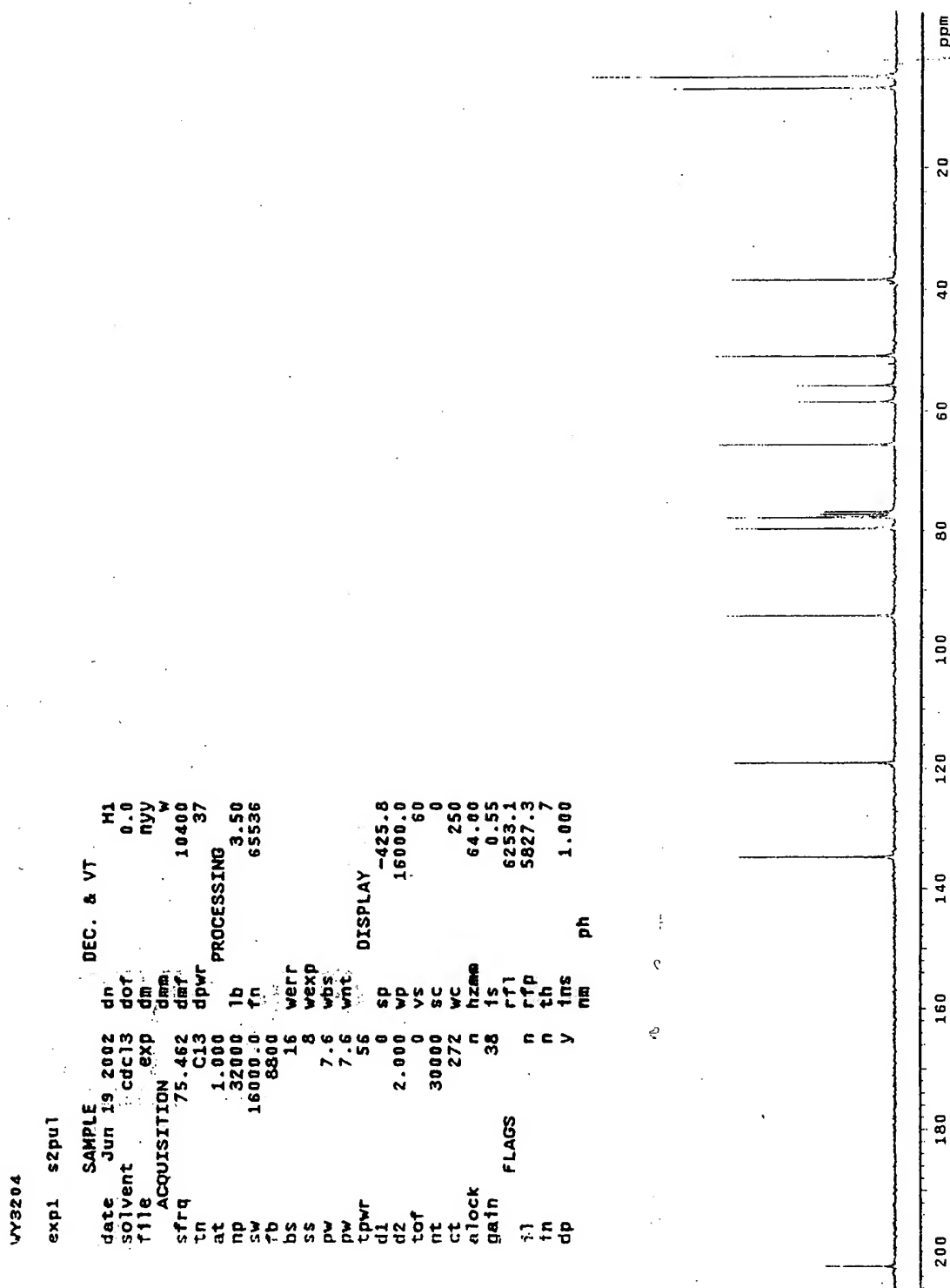


FIG. 18

SAMPLE

FIG. 19

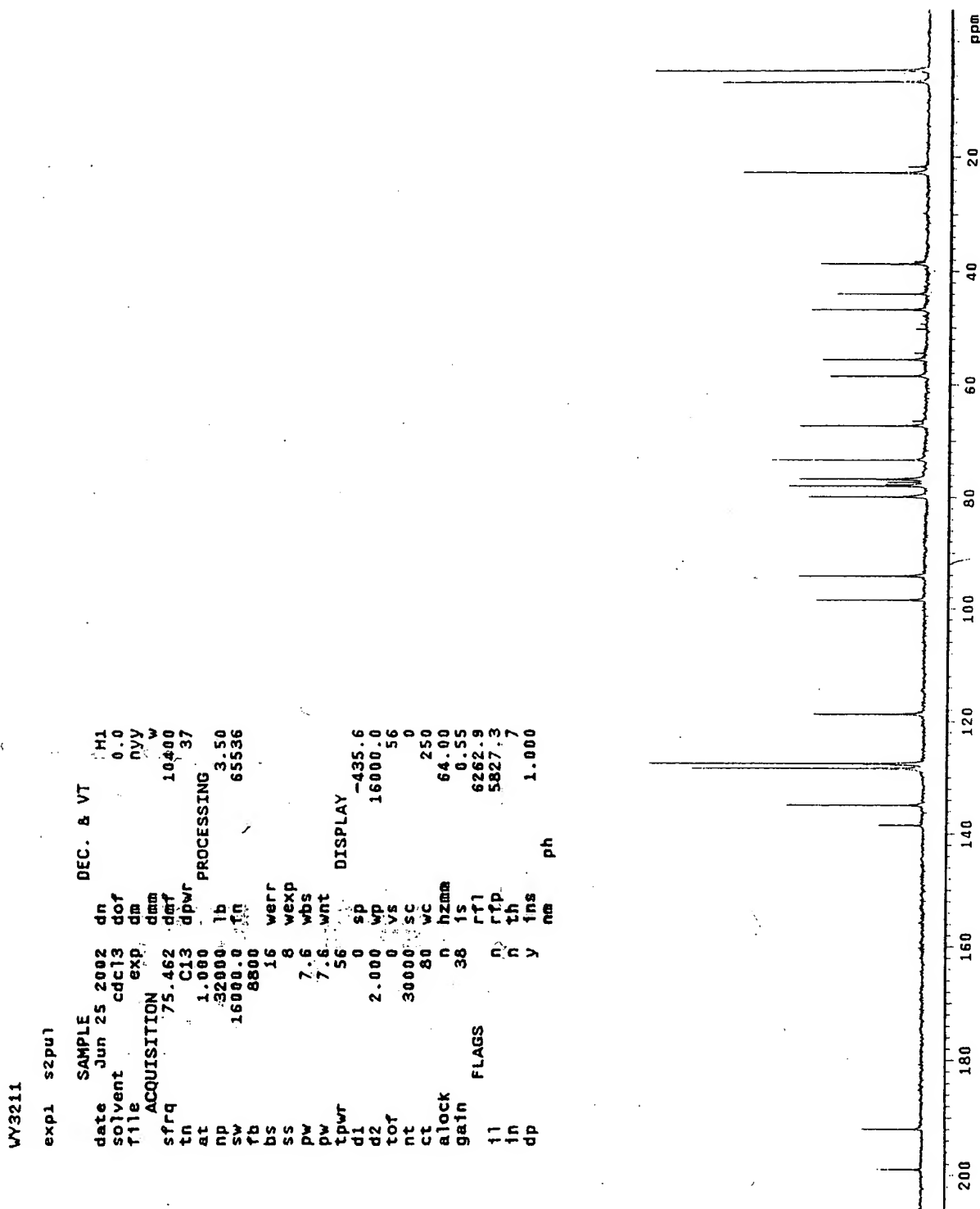


FIG. 20

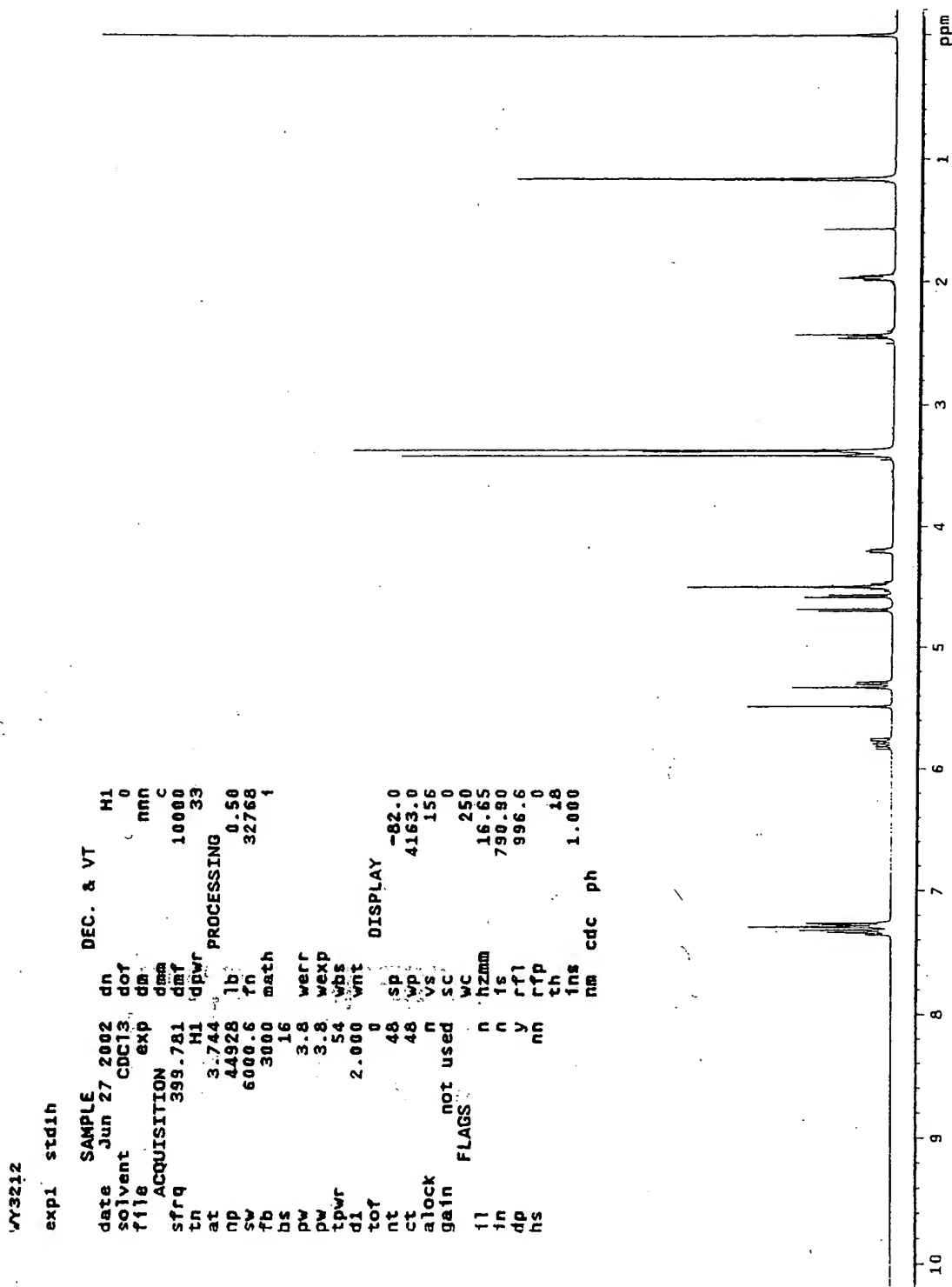


FIG. 21



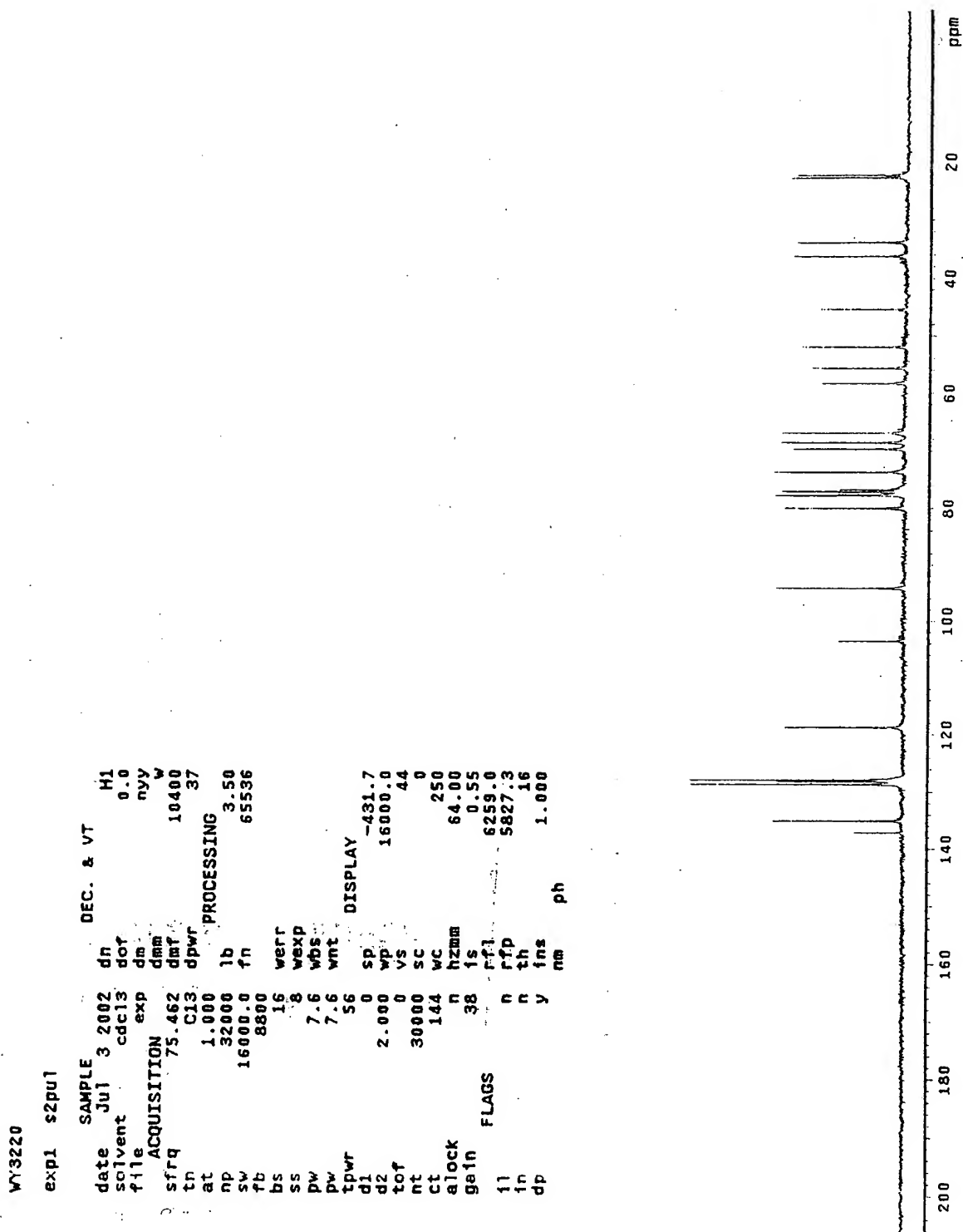


FIG. 24

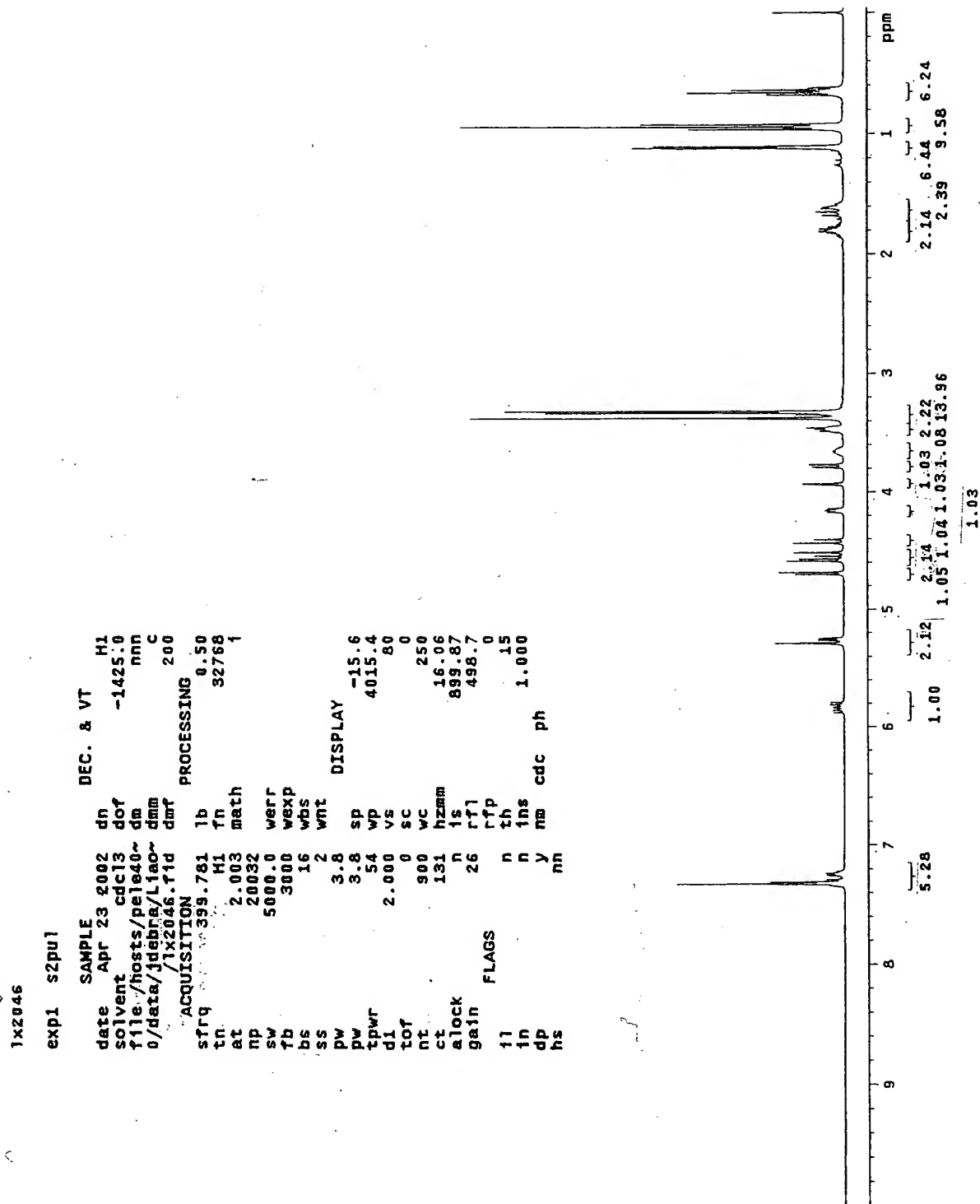


FIG. 25

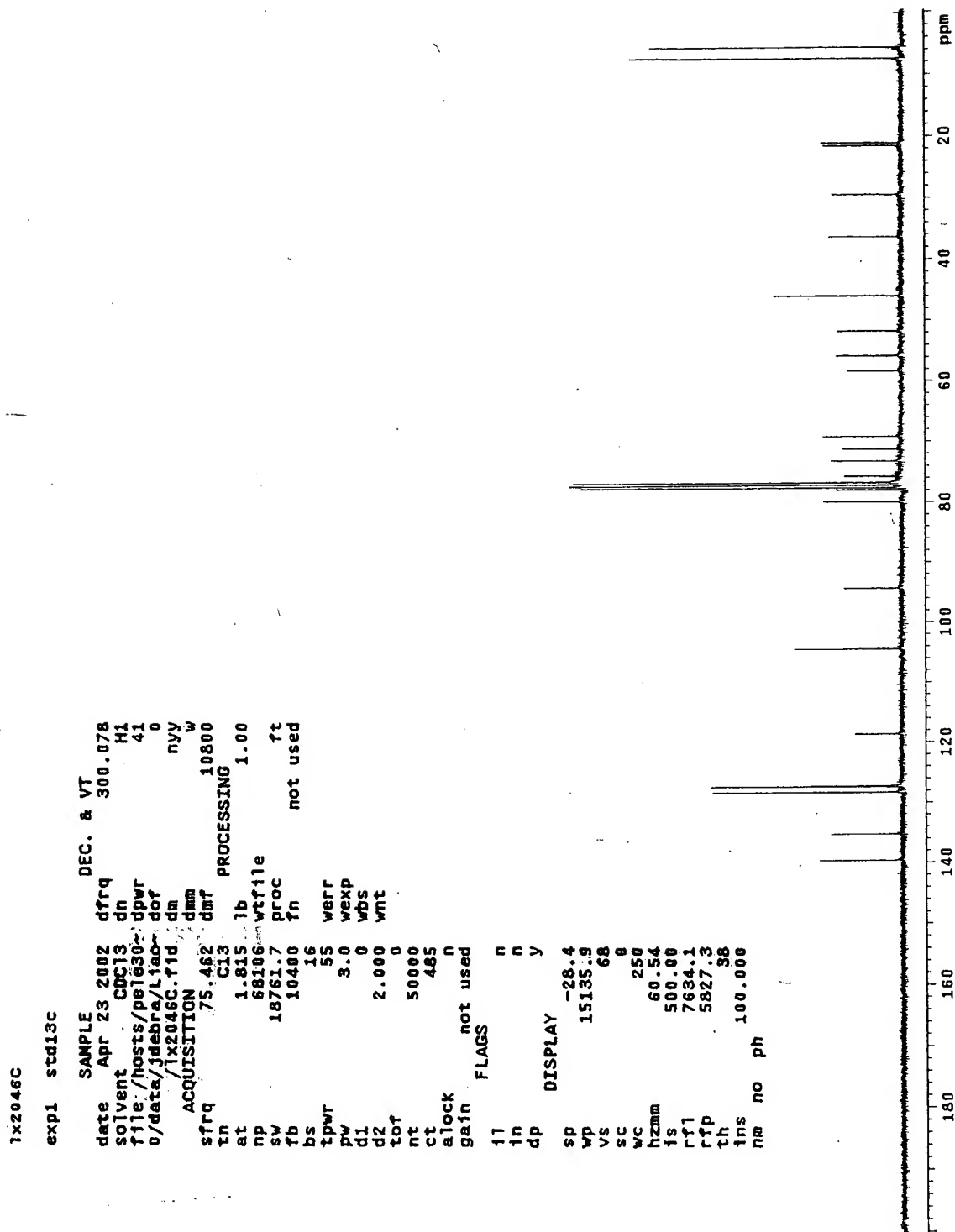


FIG. 26

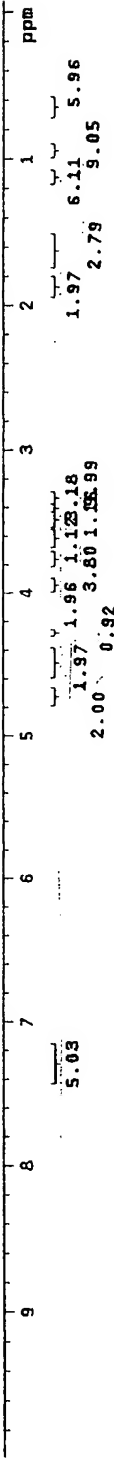


FIG. 27

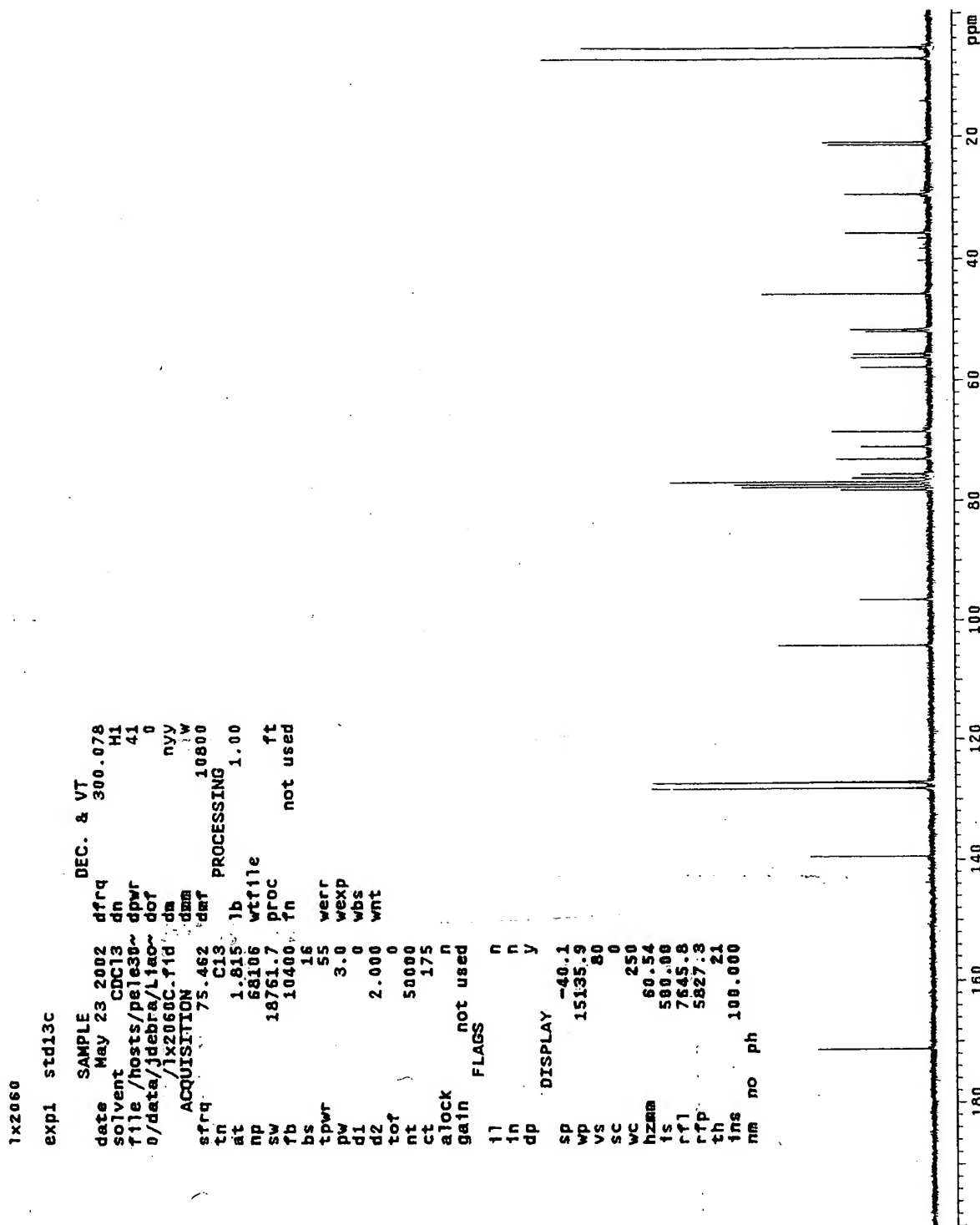


FIG. 28

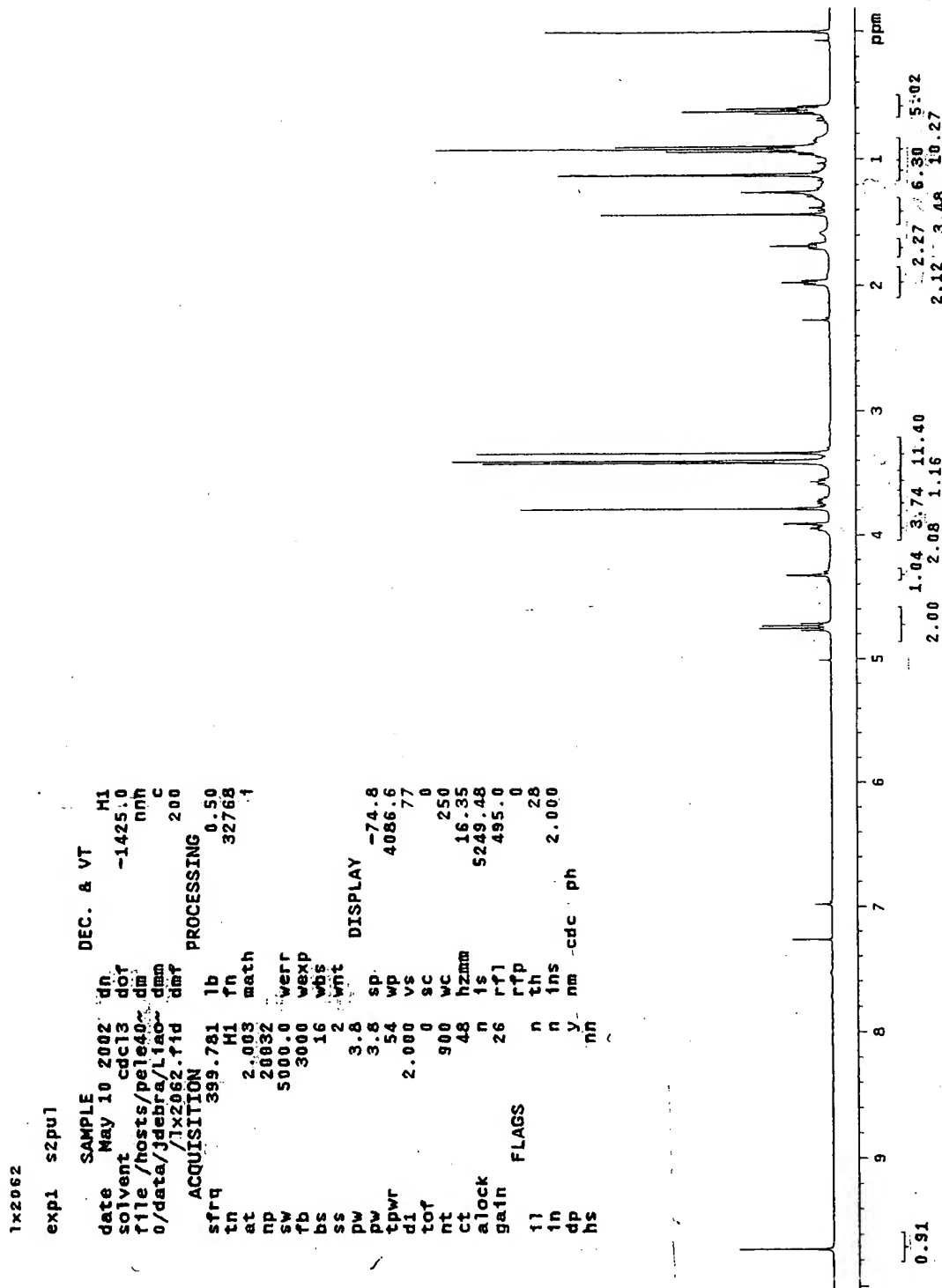


FIG.29

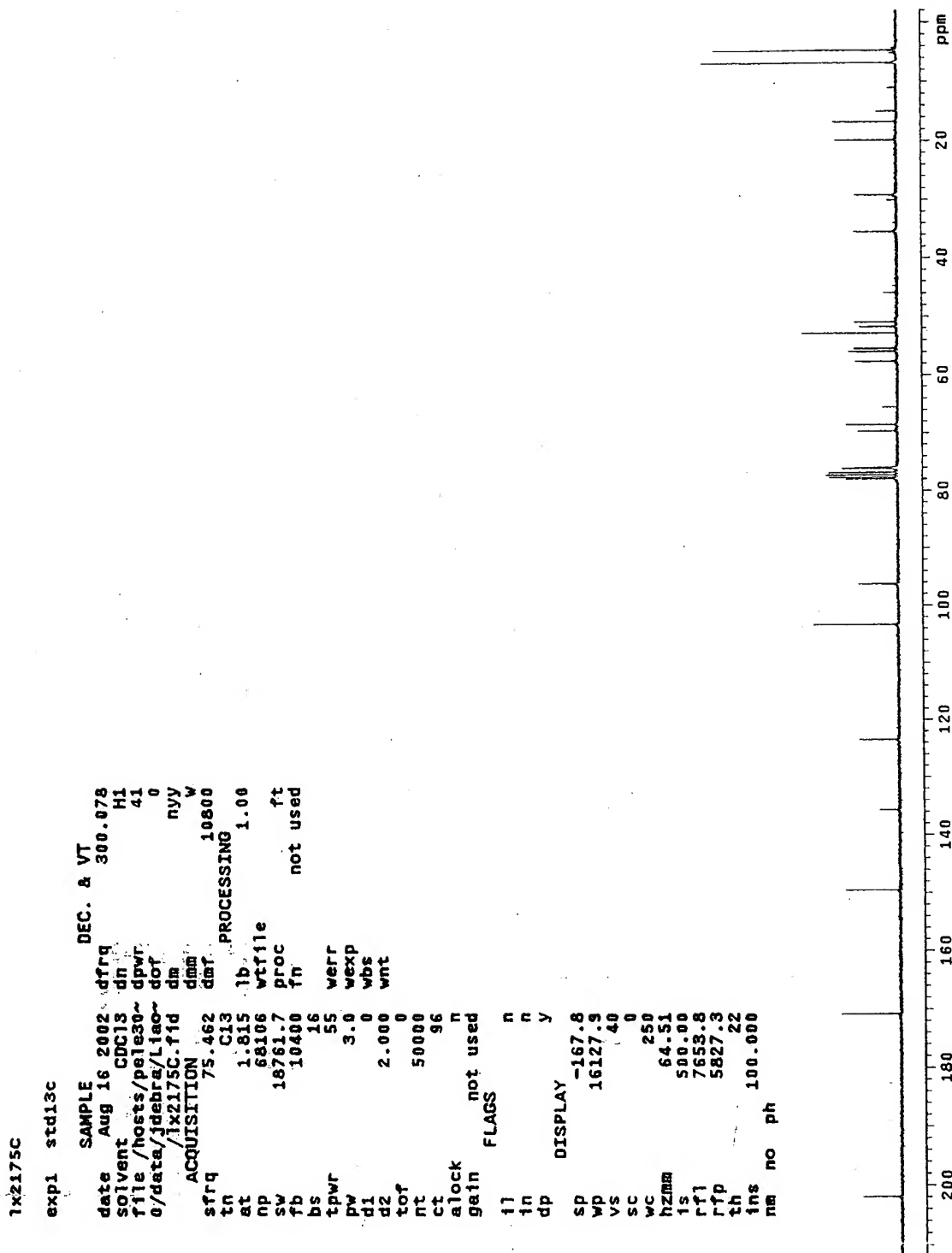


FIG. 30

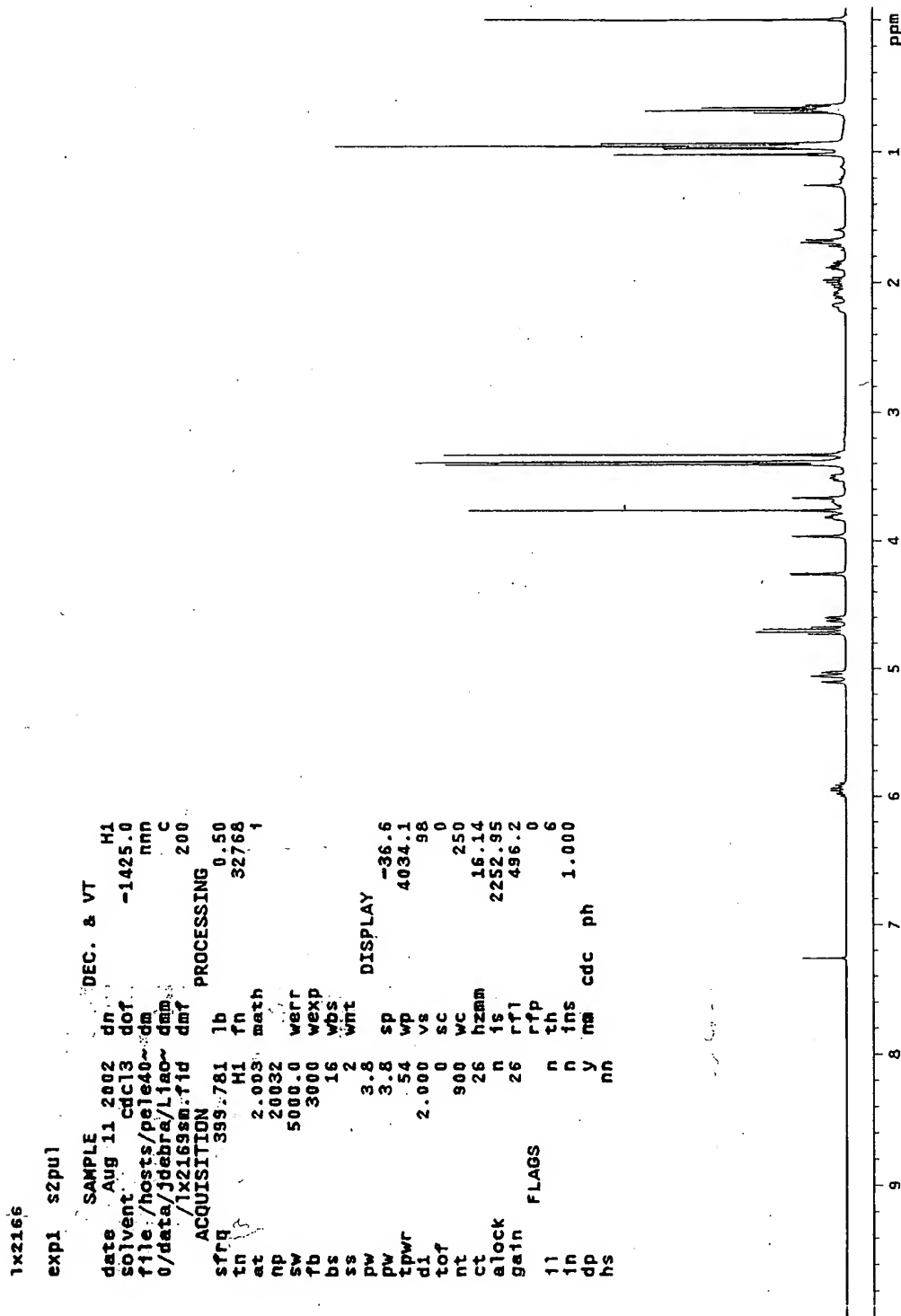


FIG. 31

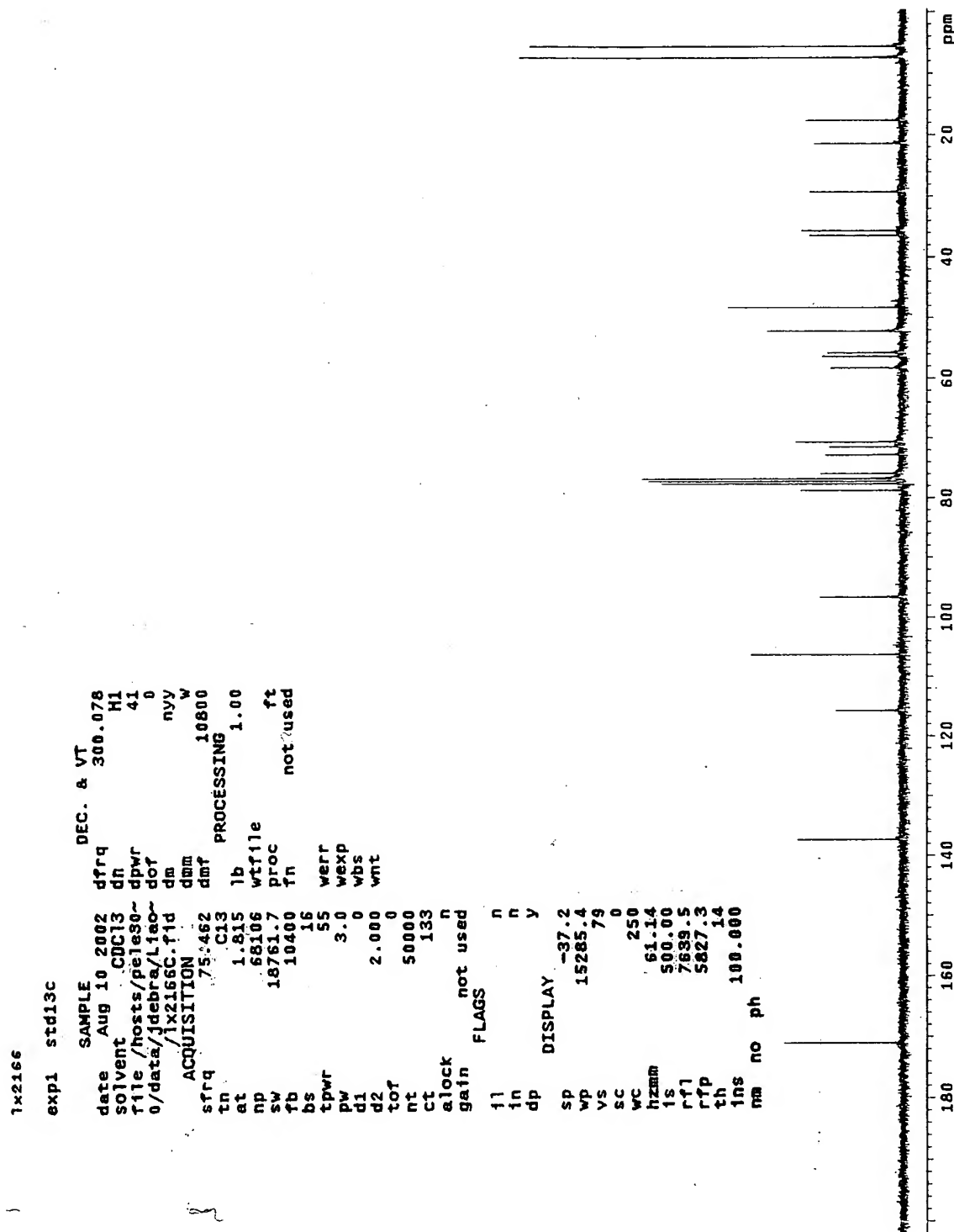


FIG. 32

24
400 MHz
CDCl₃

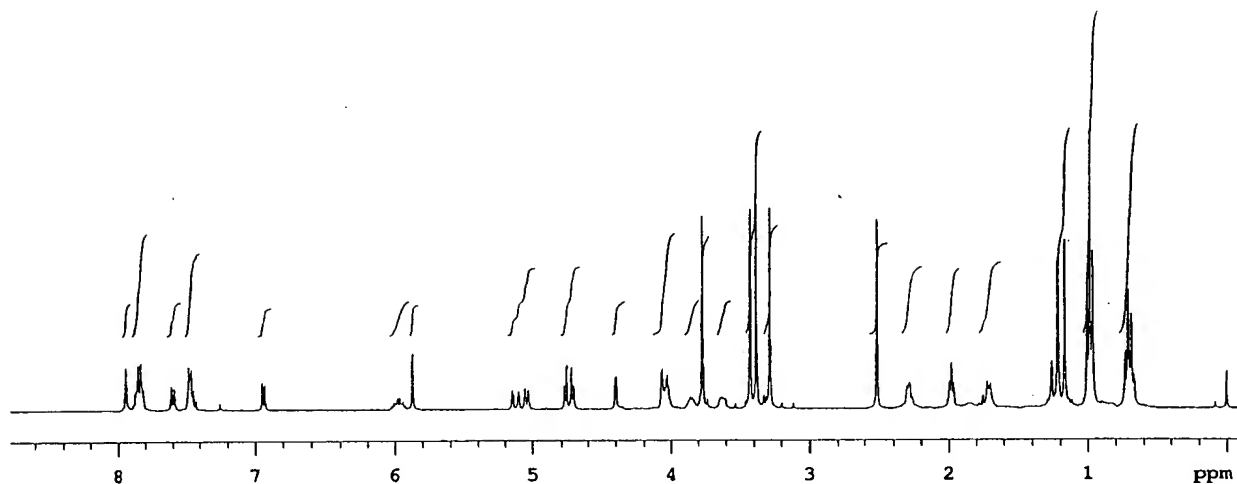


FIG. 33

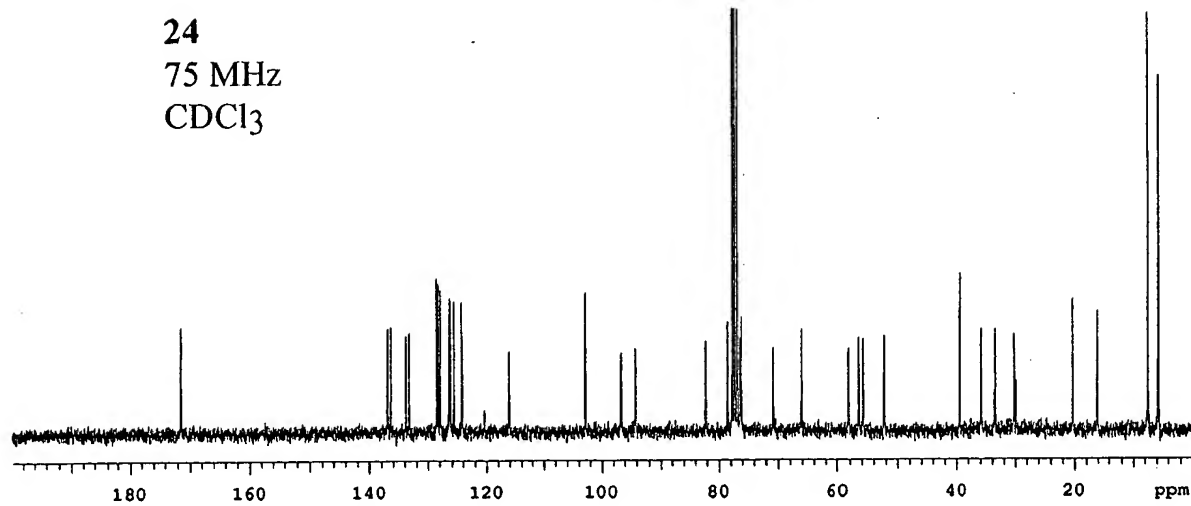


FIG. 34

24 1D-NOE Irradiation at 5.87 ppm
400 MHz
CDCl₃

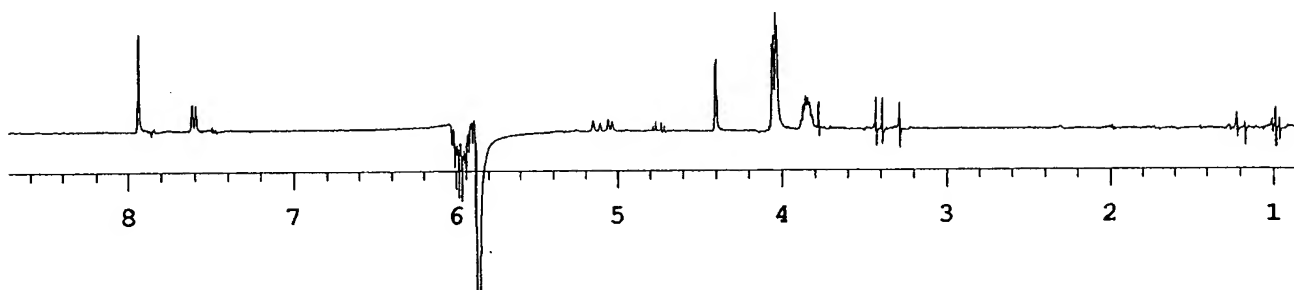


FIG. 35

24 1D-NOE Irradiation at 1.22 ppm
400 MHz
CDCl₃

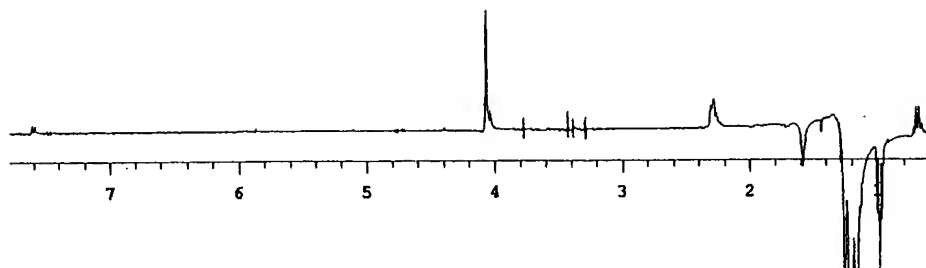


FIG. 36

29
400 MHz
CDCl₃

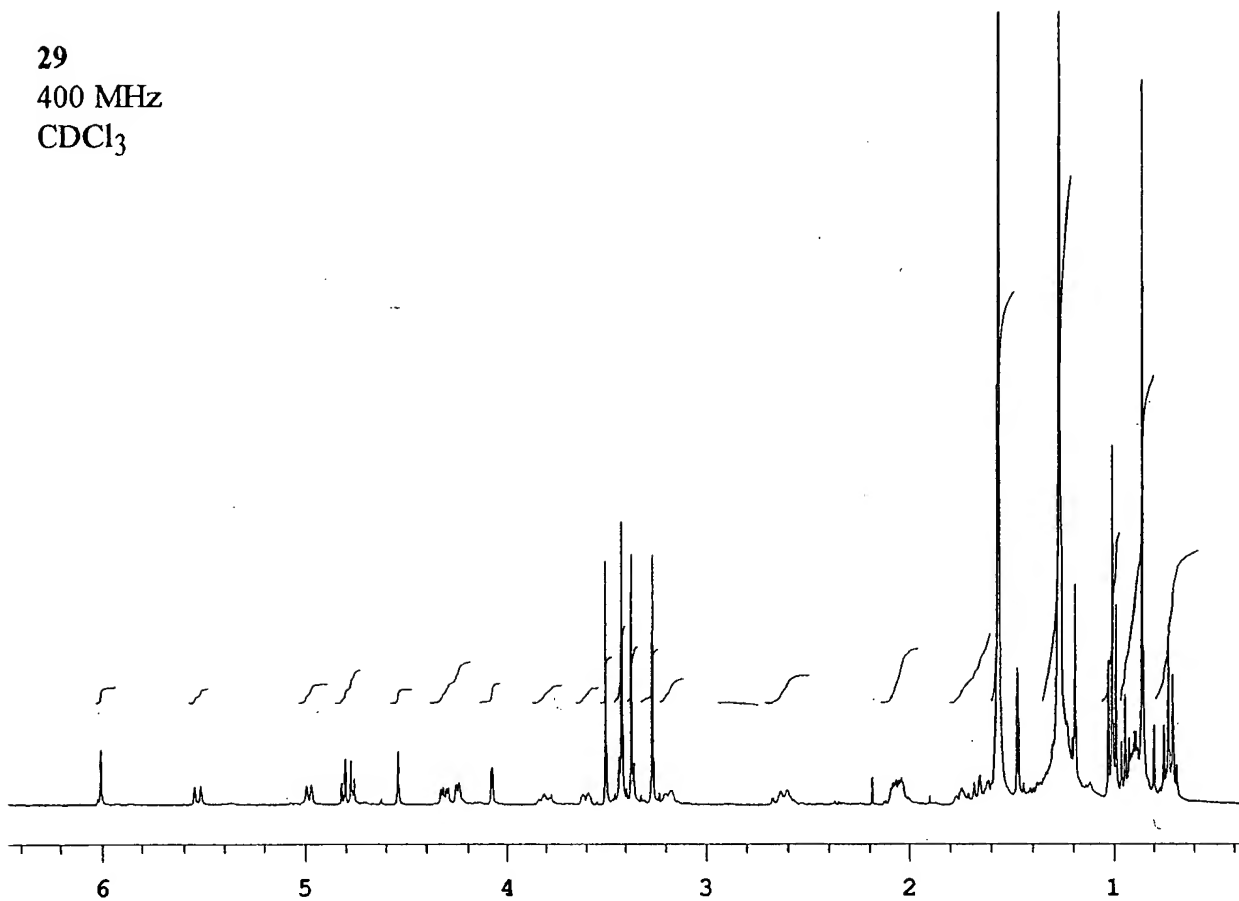


FIG. 37

29 1D-NOE Irradiation at 5.53 ppm
400 MHz
CDCl₃

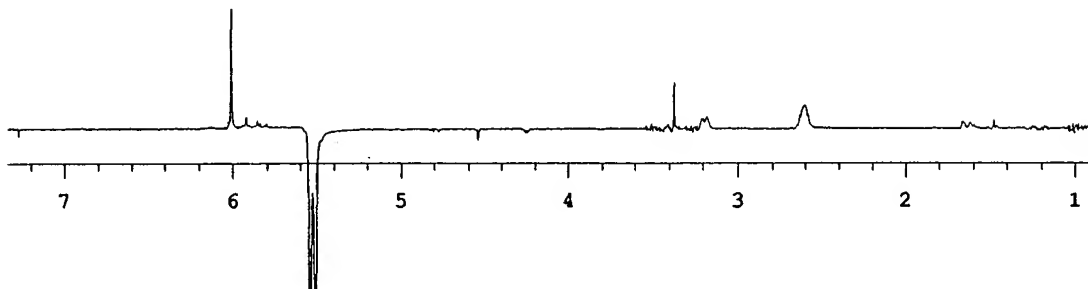


FIG. 38

29 1D-NOE Irradiation at 4.54 ppm
400 MHz
CDCl₃

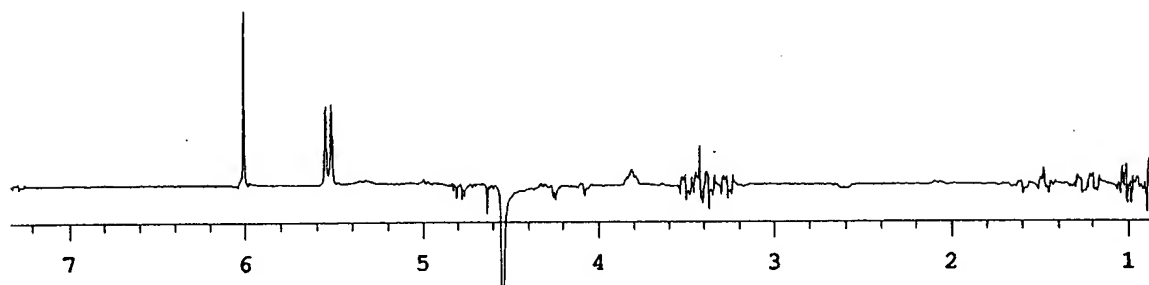


FIG. 39

Compound 29 2D NOE
400MHz CDCl₃

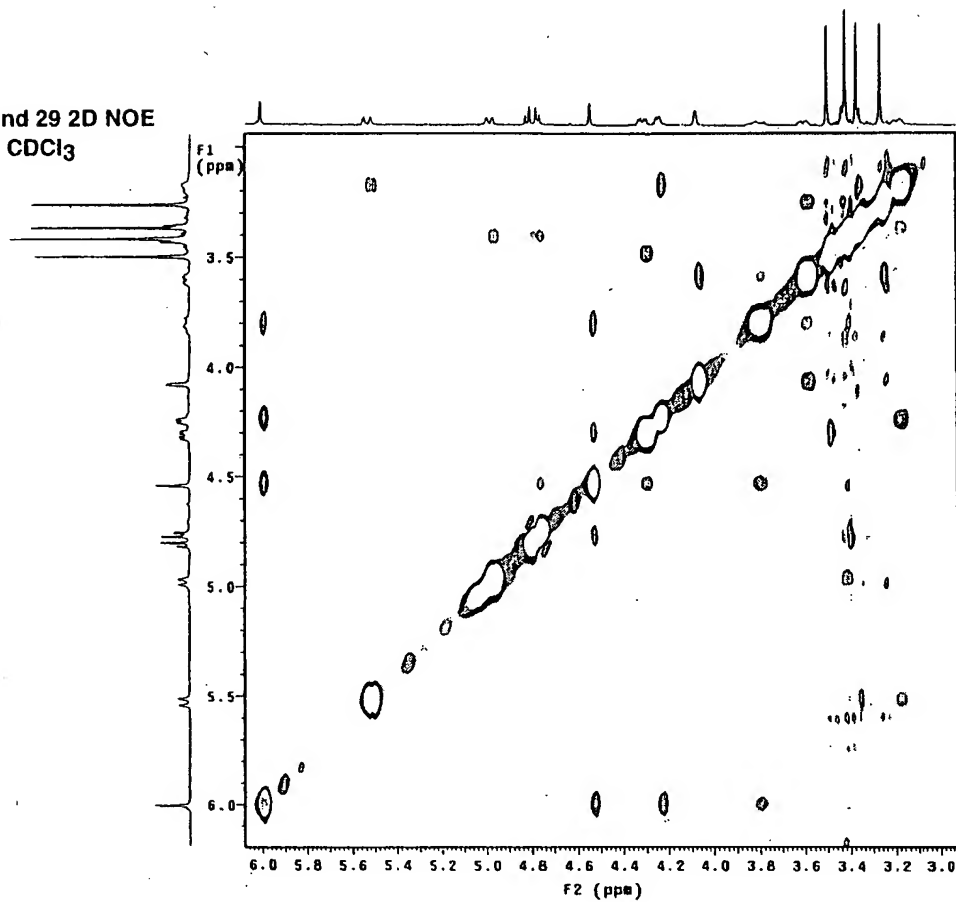


FIG. 40

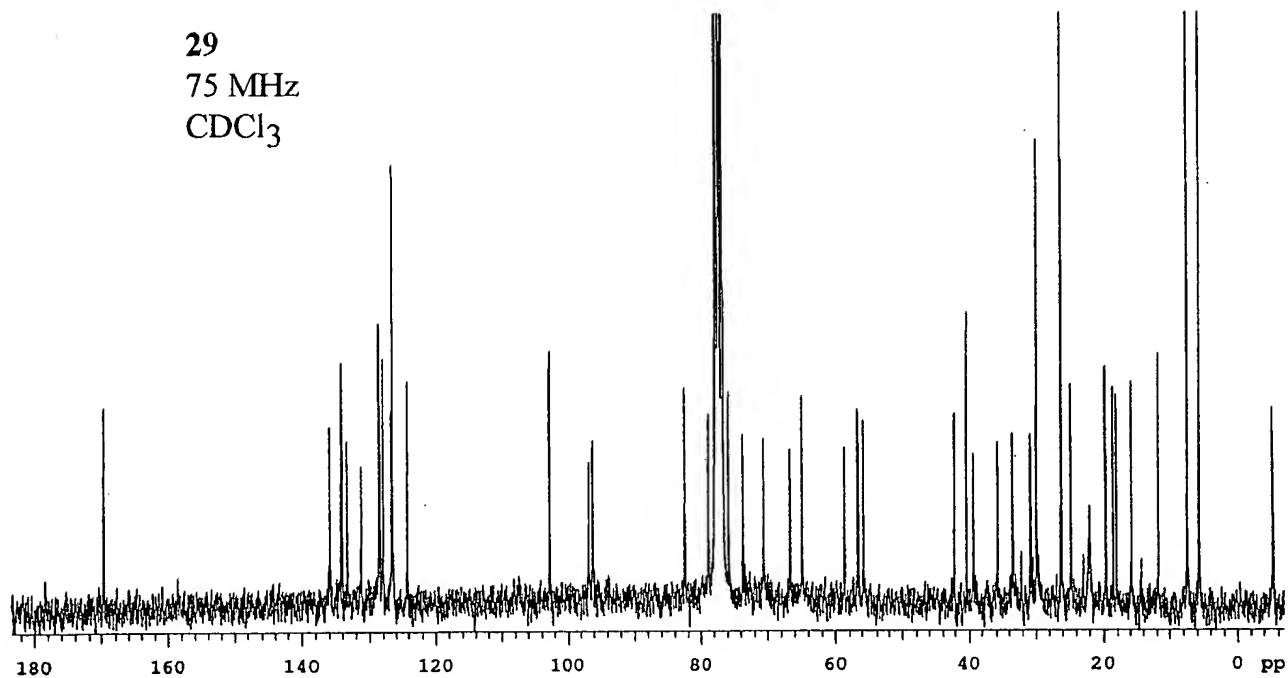


FIG. 41

30
400 MHz
CDCl₃

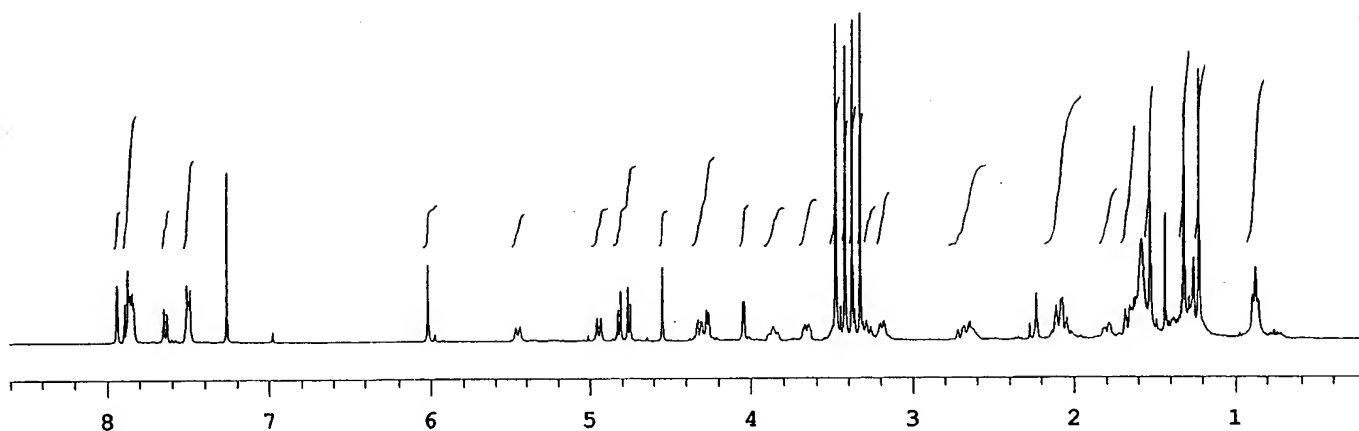


FIG. 42

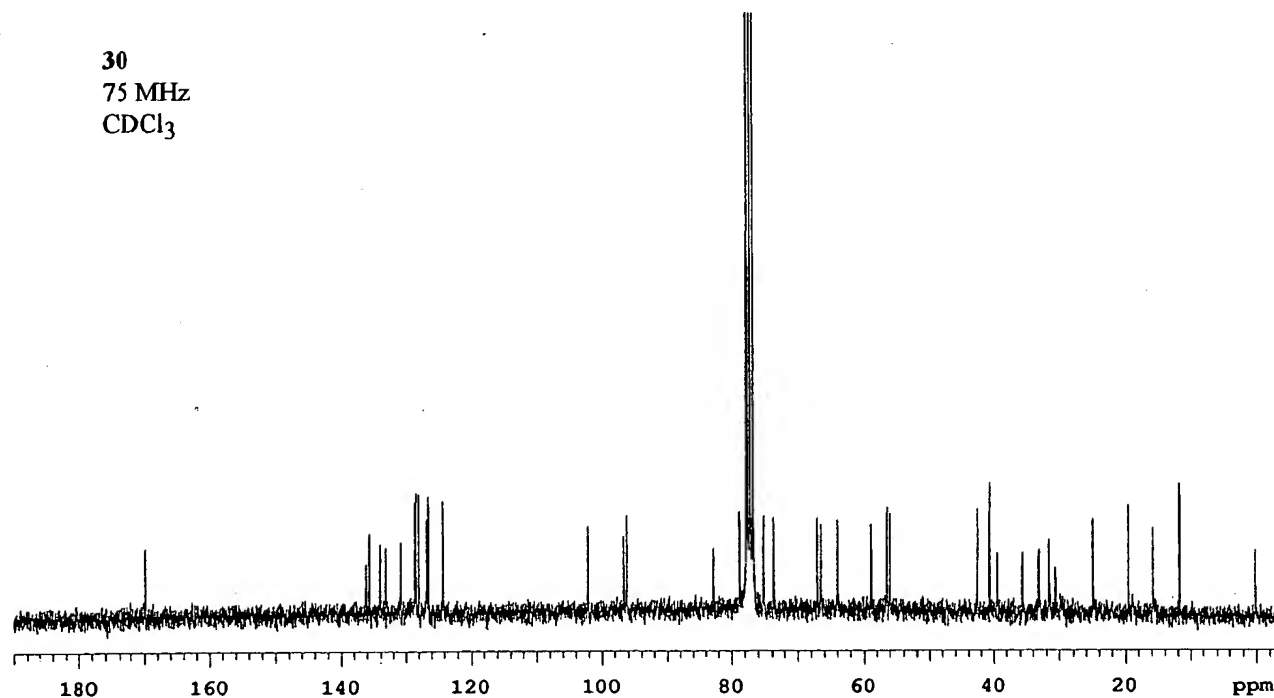


FIG. 43

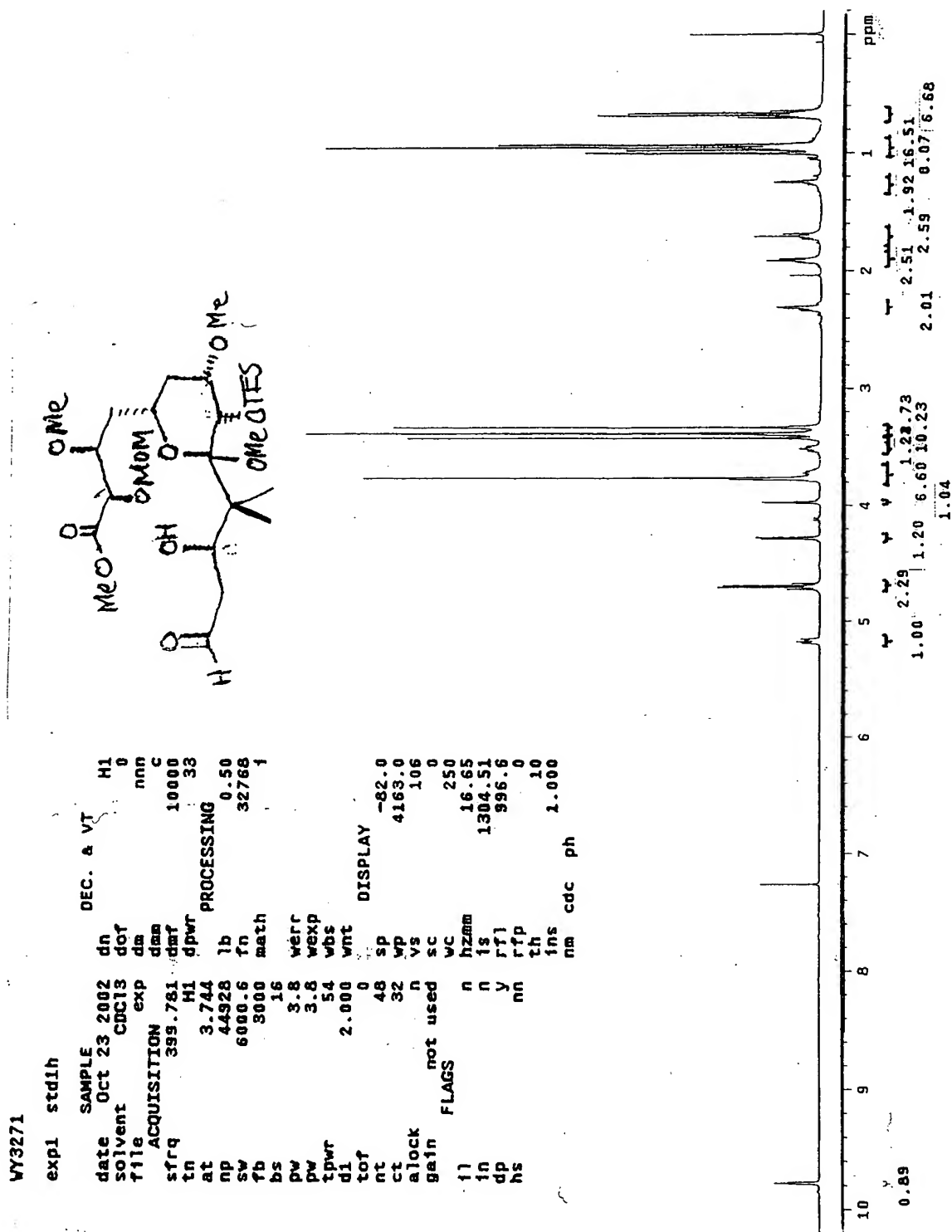


FIG. 44

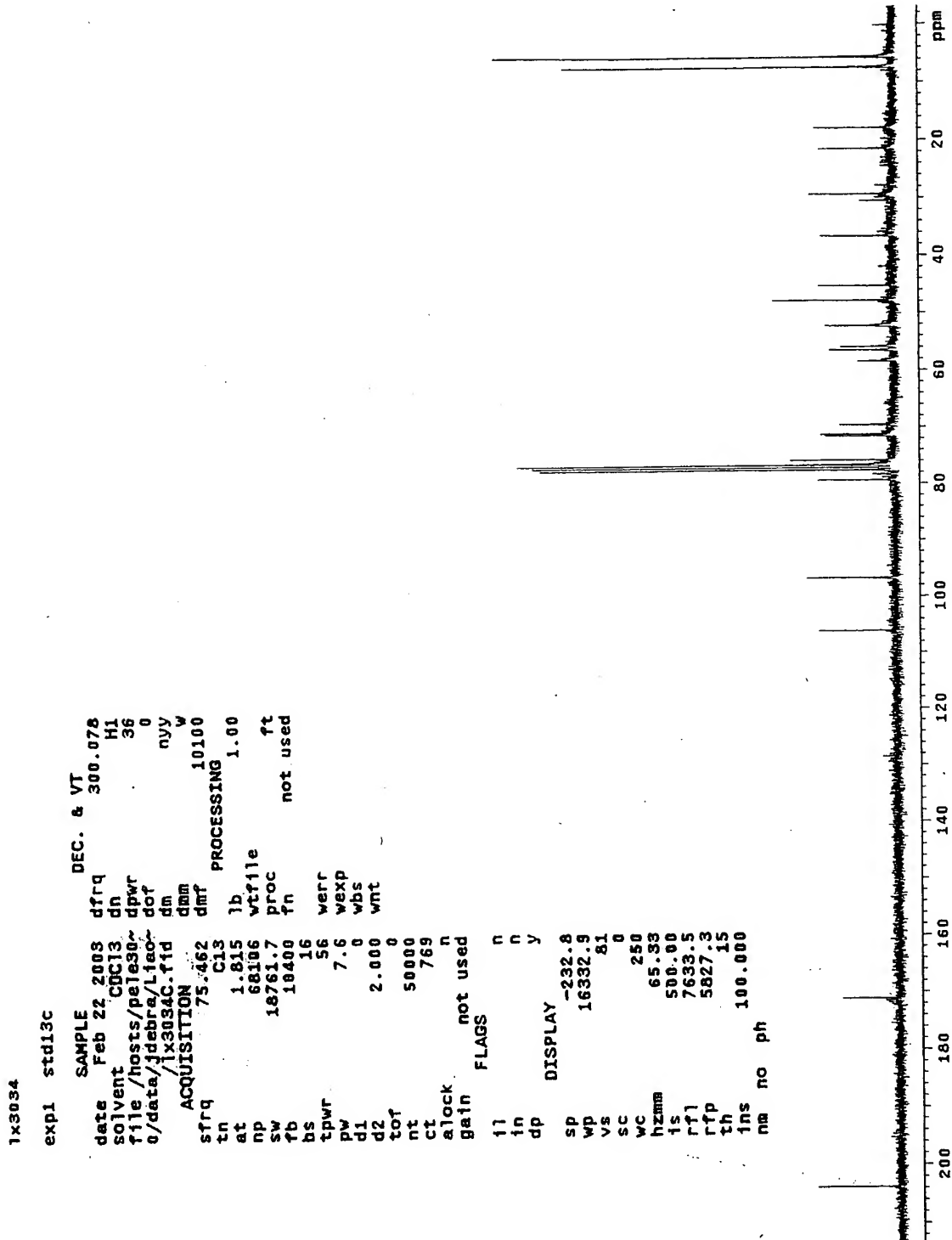


FIG. 45

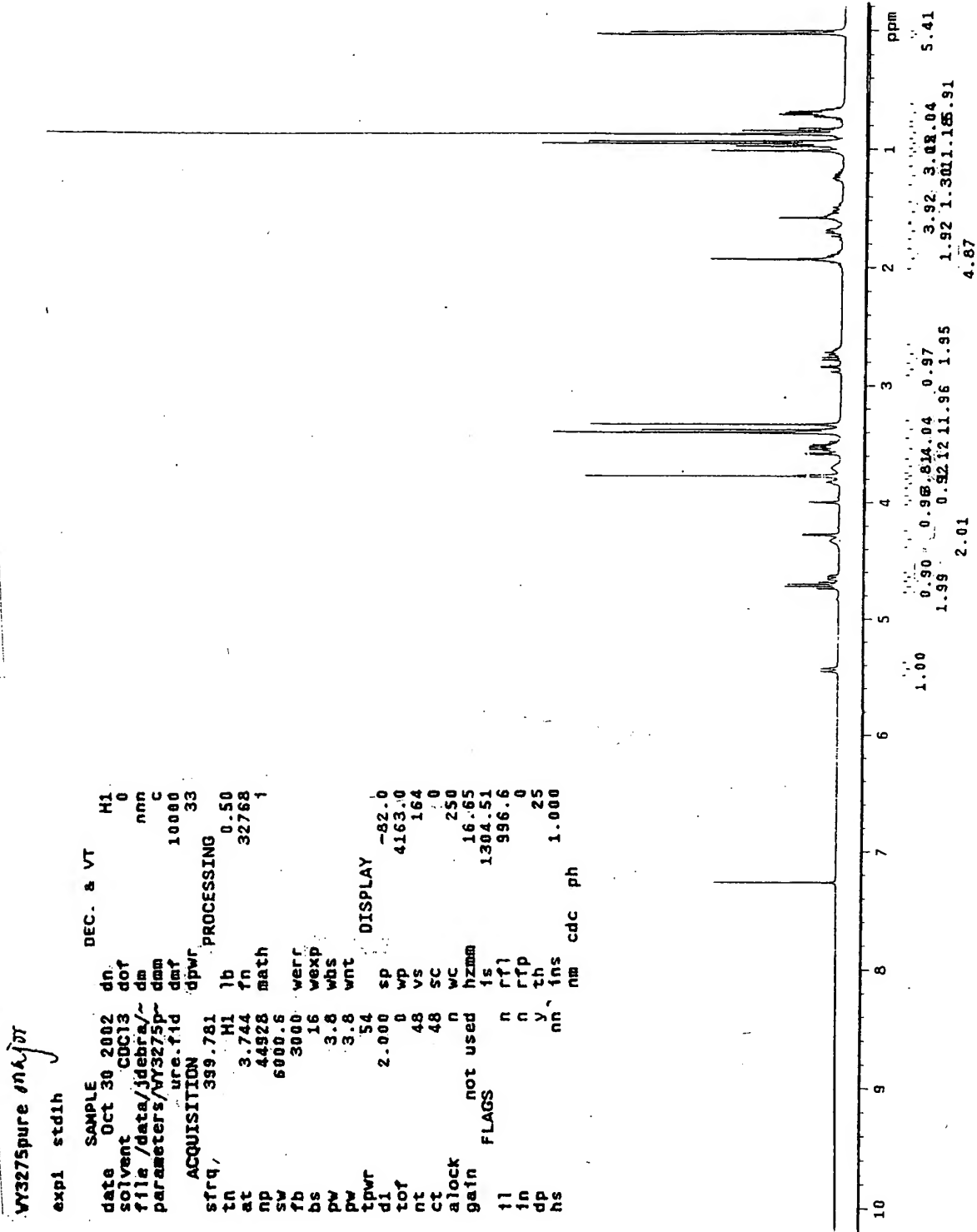


FIG. 46

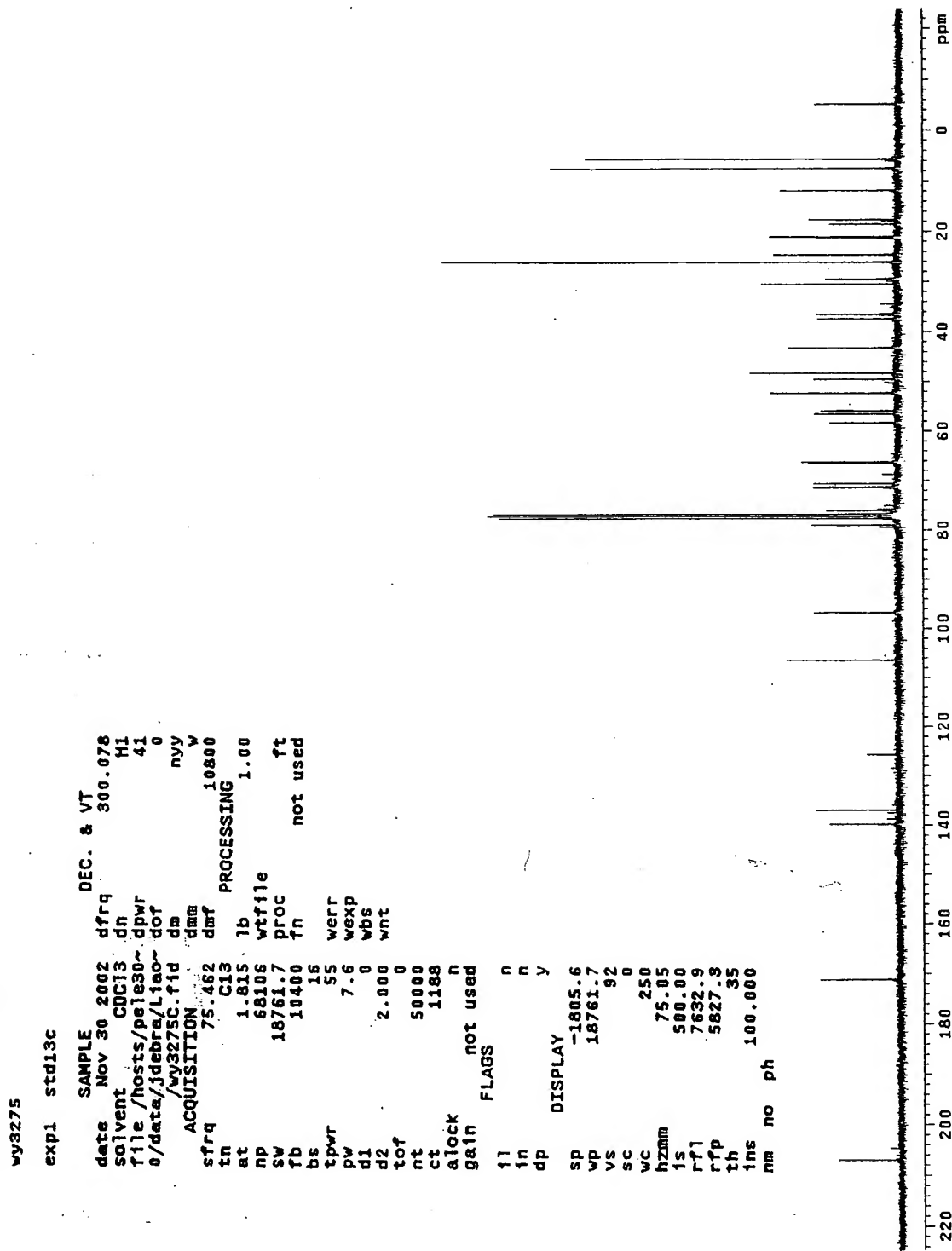


FIG. 47

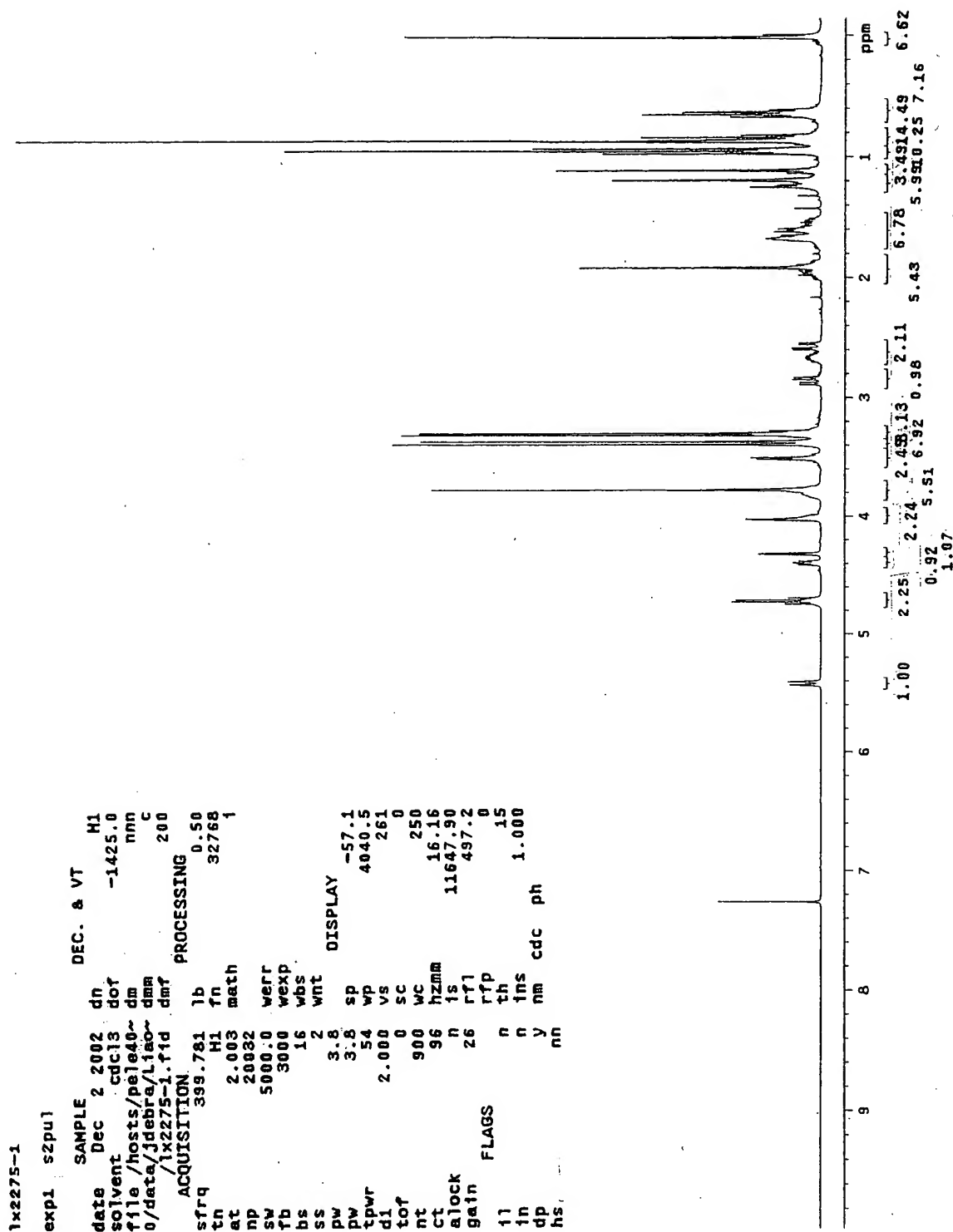


FIG. 48

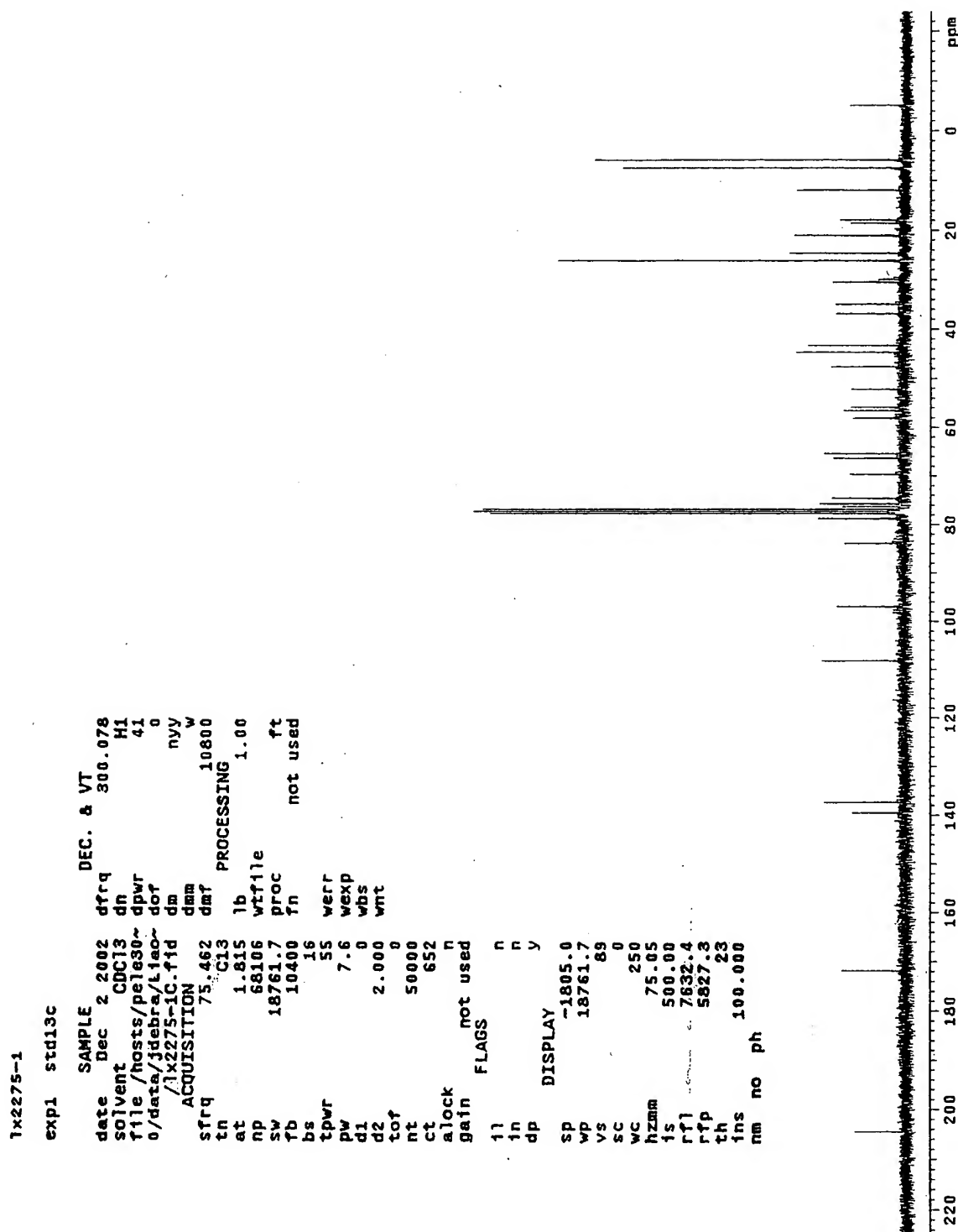


FIG. 49

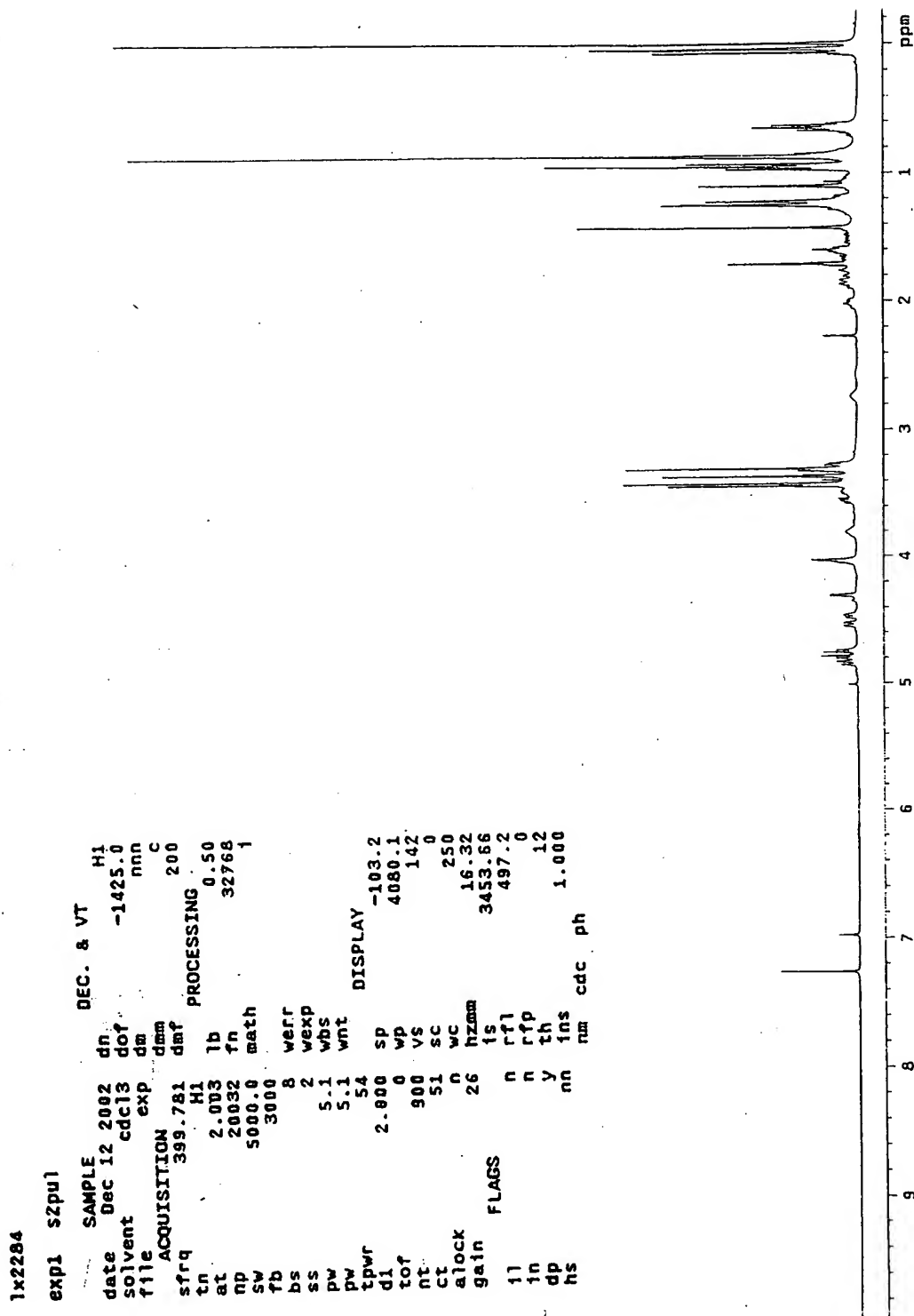


FIG. 50

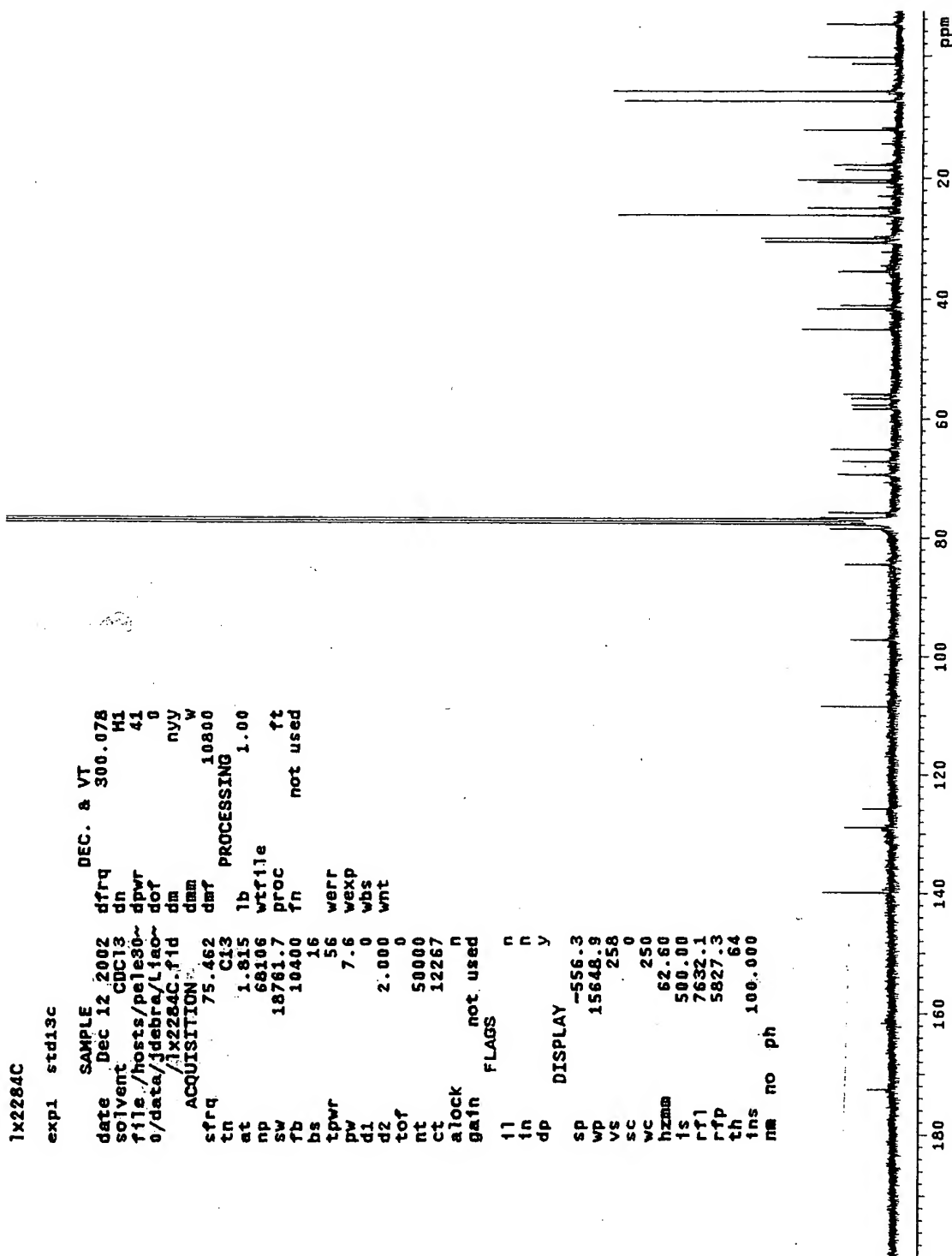


FIG. 51

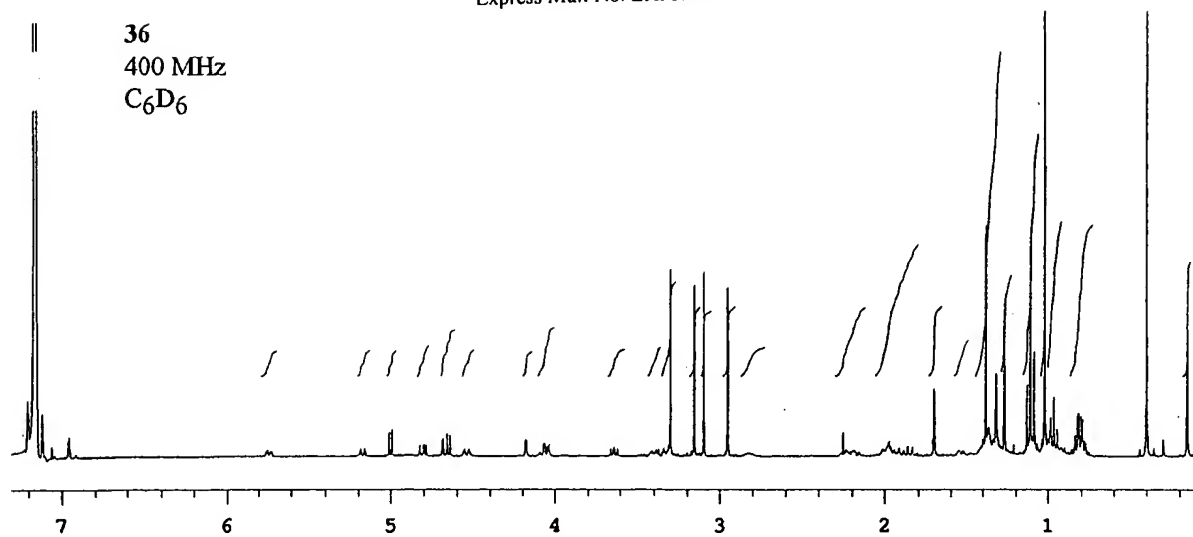


FIG. 52

36 1D-NOE Irradiation at 5.74 ppm
400 MHz
C₆D₆

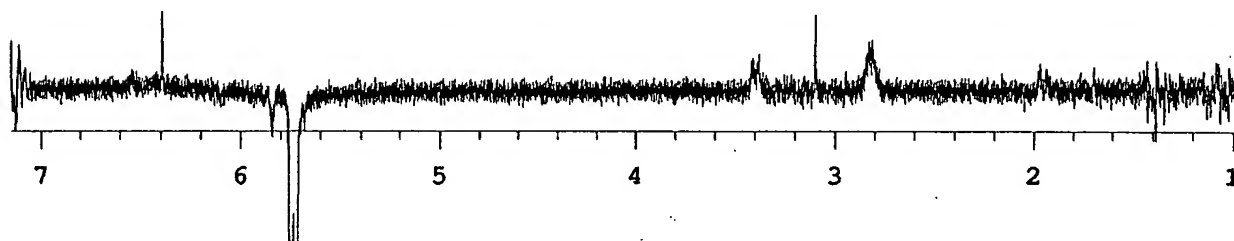


FIG. 53

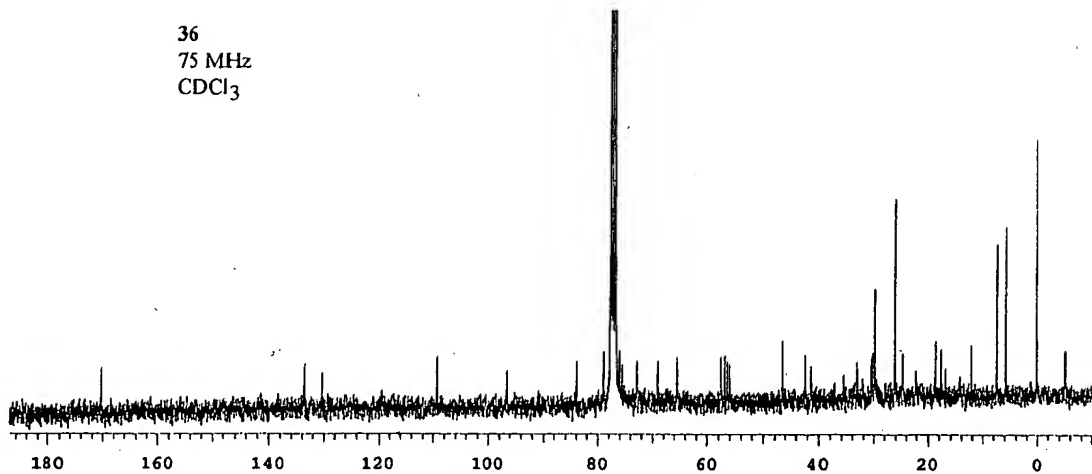


FIG. 54

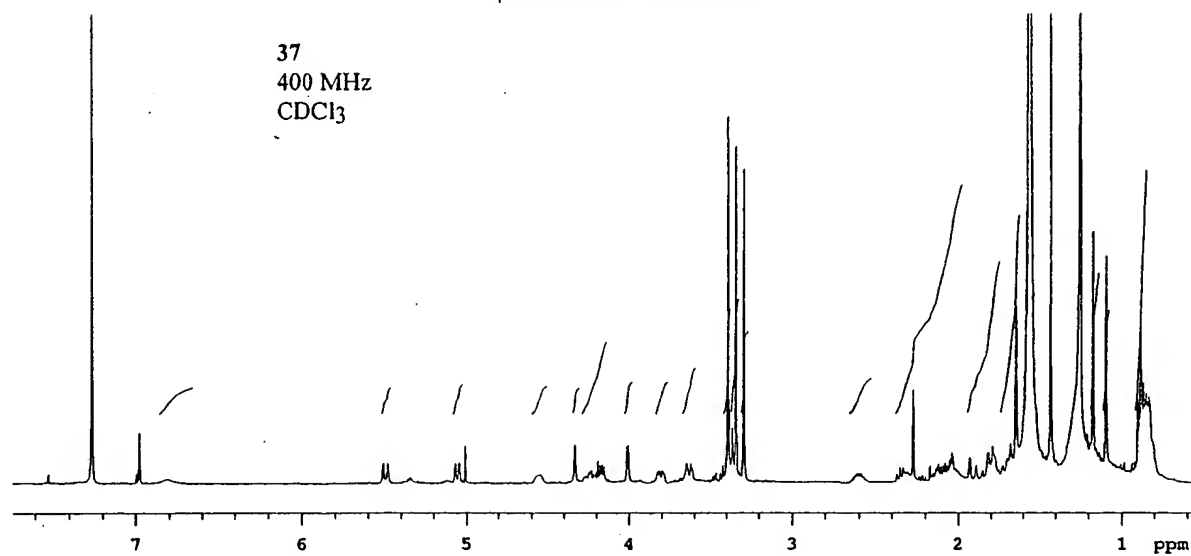


FIG. 55

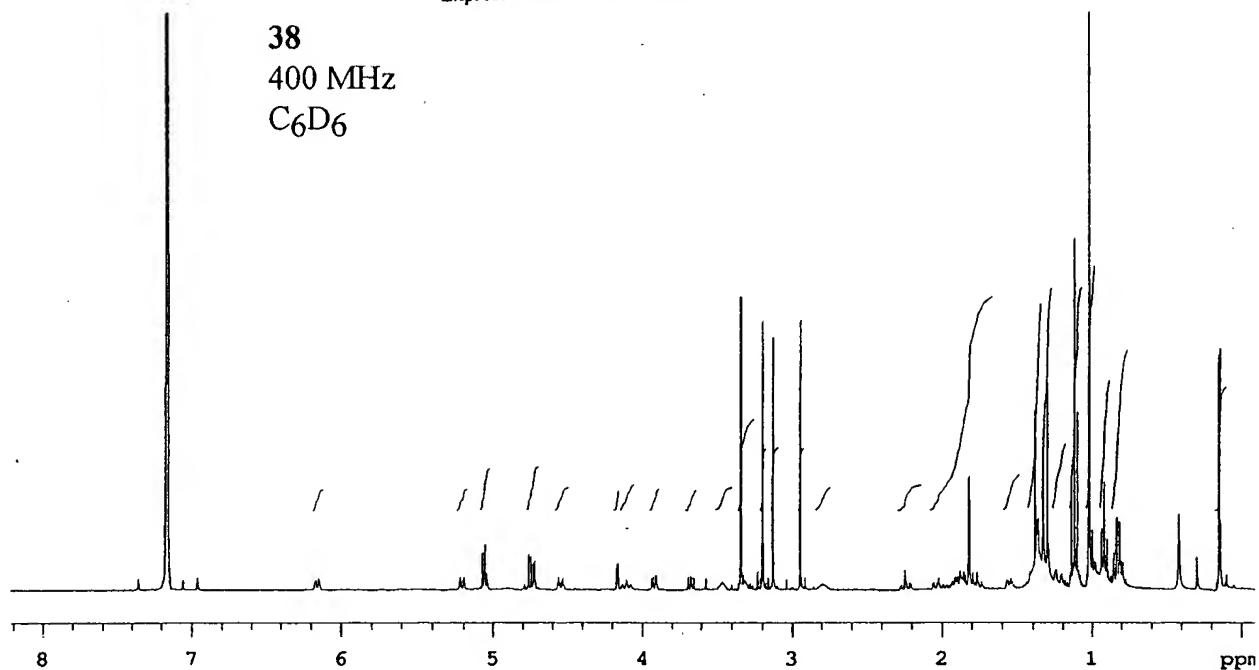


FIG. 56

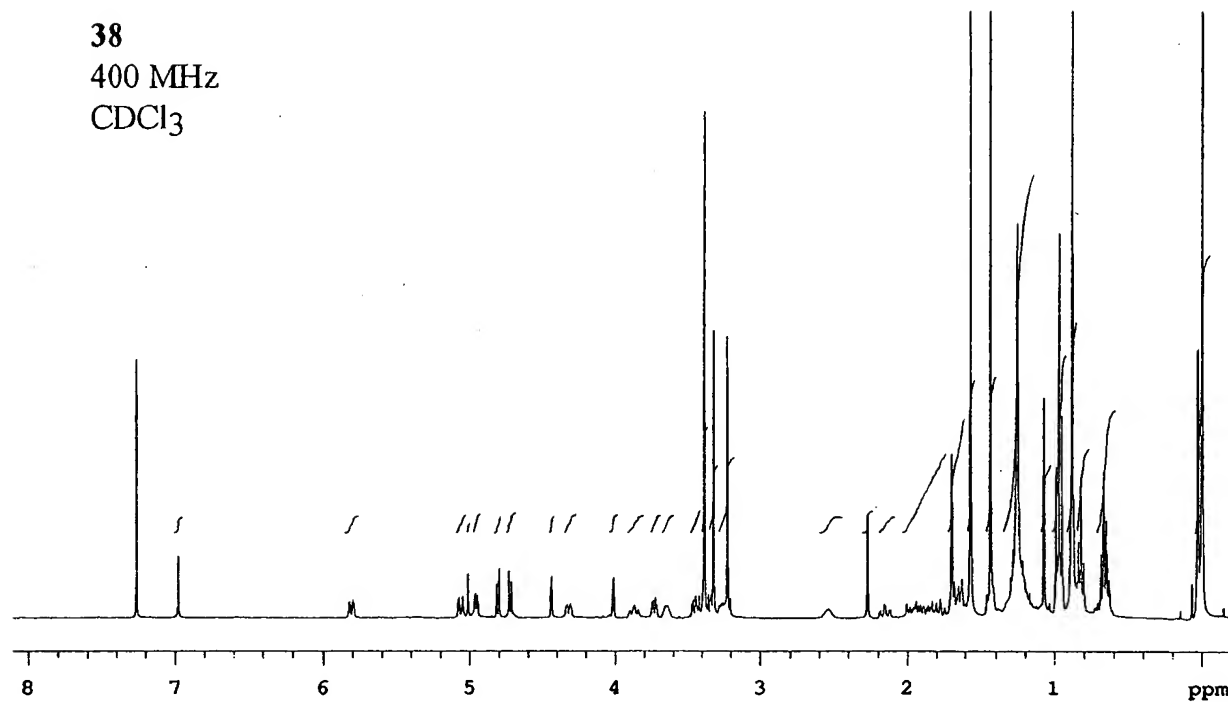


FIG. 57

38 1D-NOE Irradiation at 6.16 ppm
400 MHz
C₆D₆

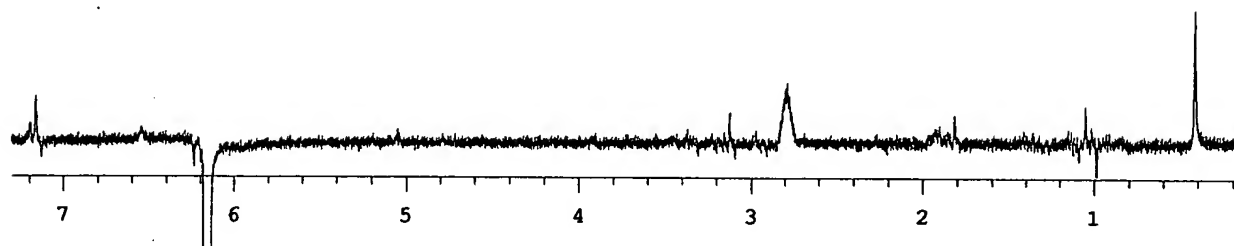


FIG. 58

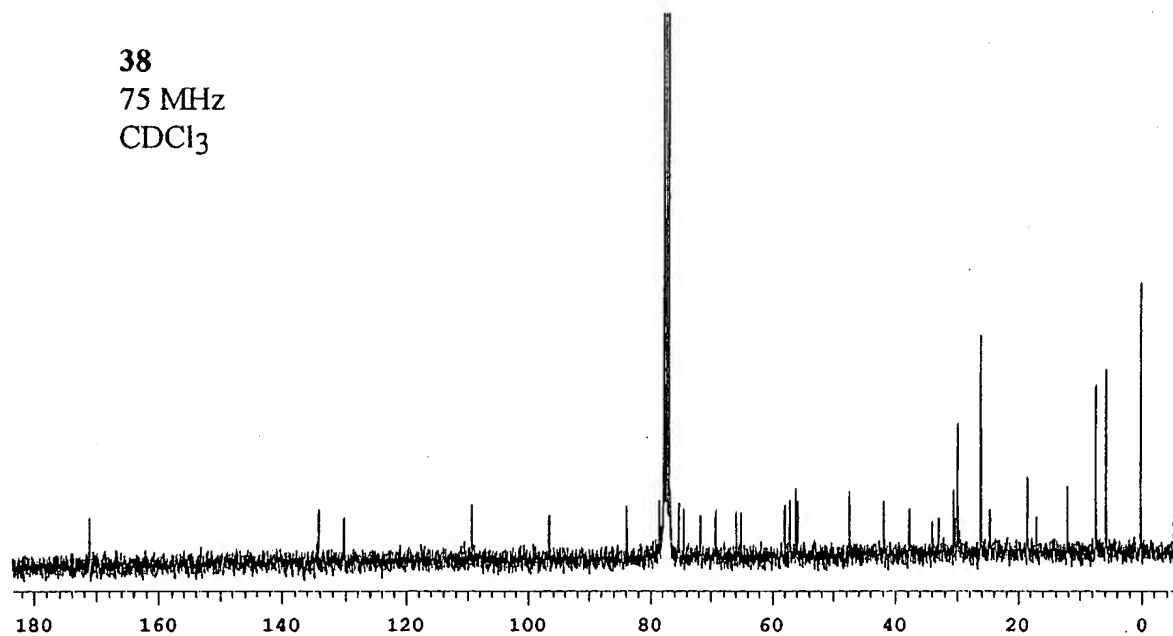


FIG. 59

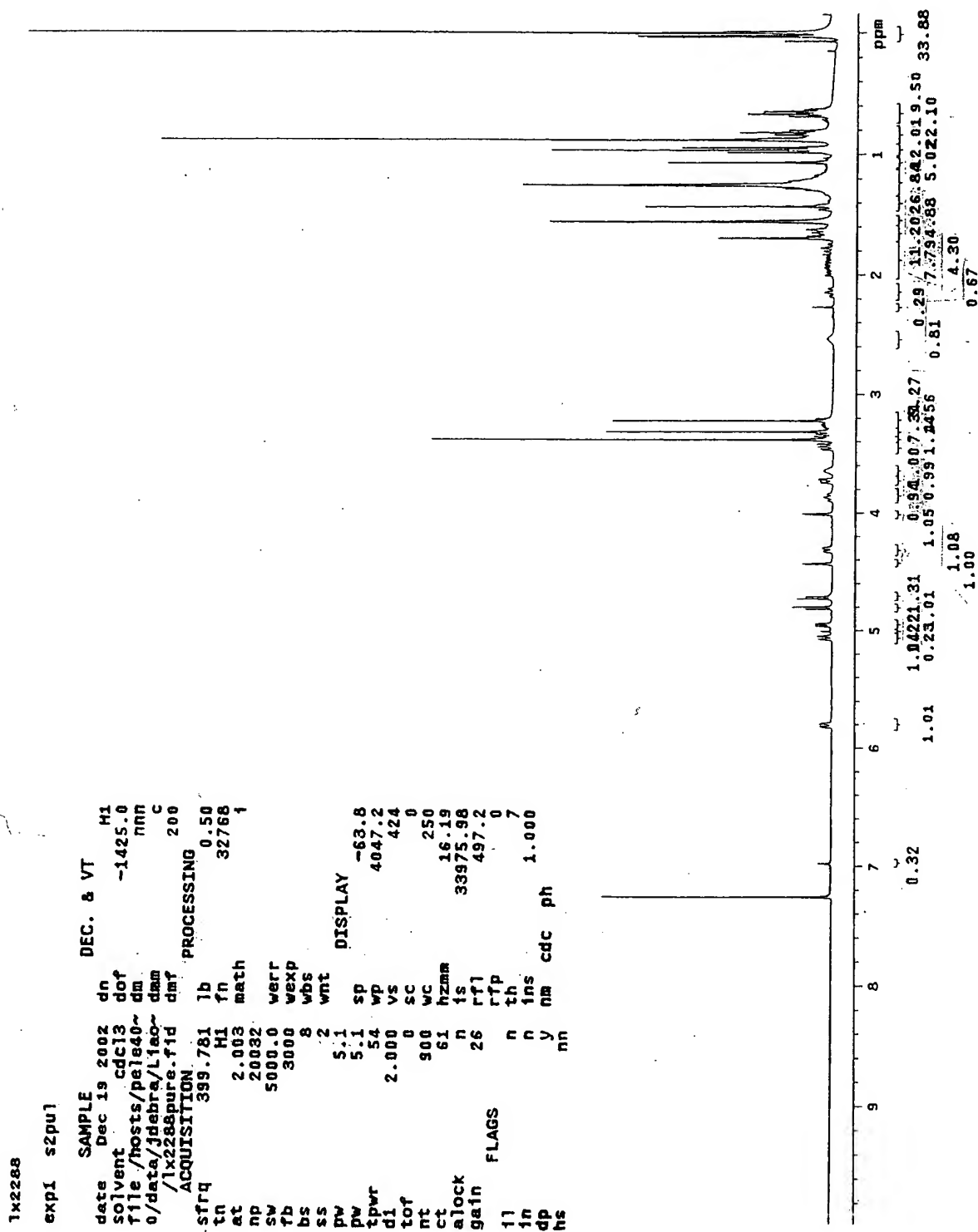


FIG. 60

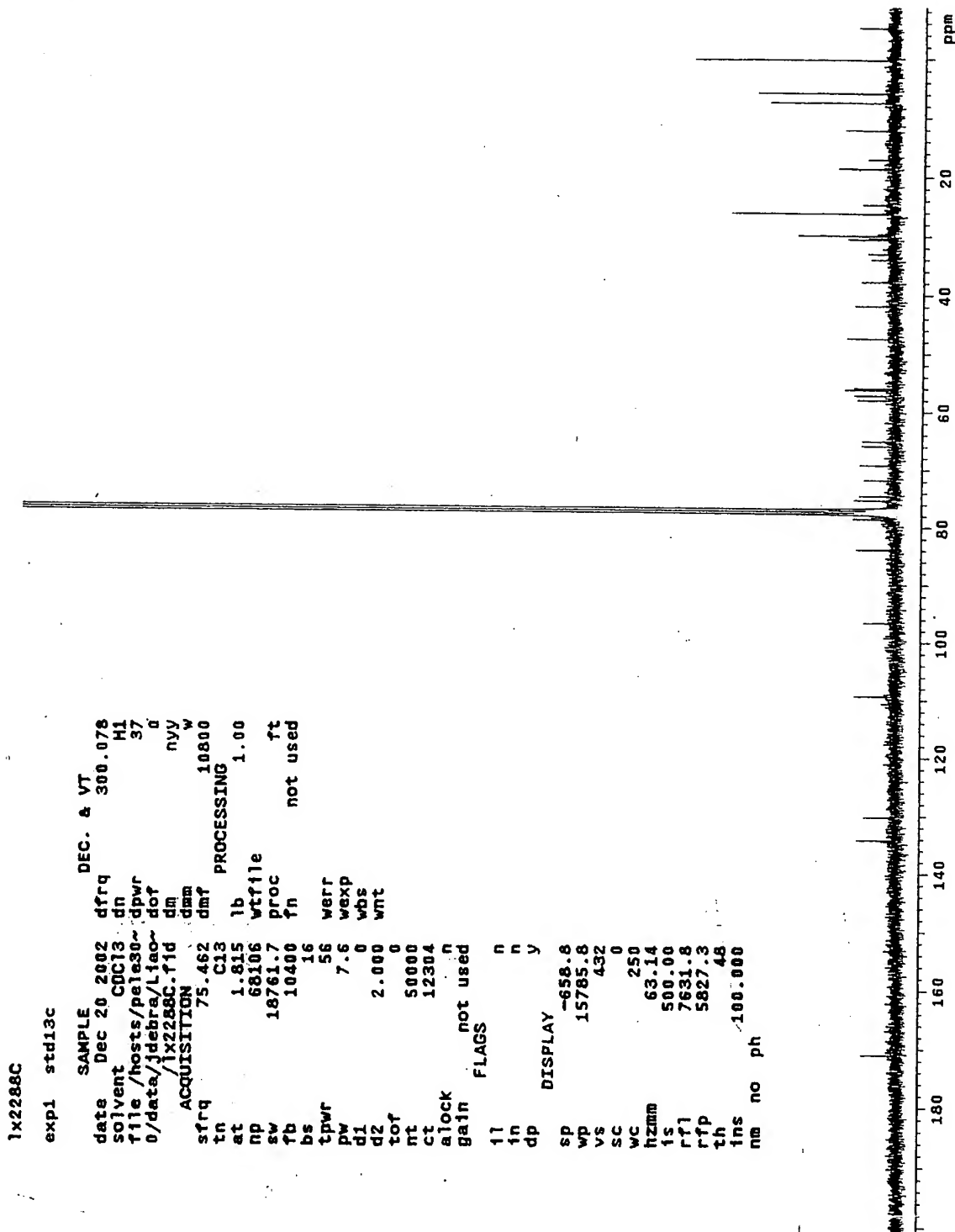


FIG. 61

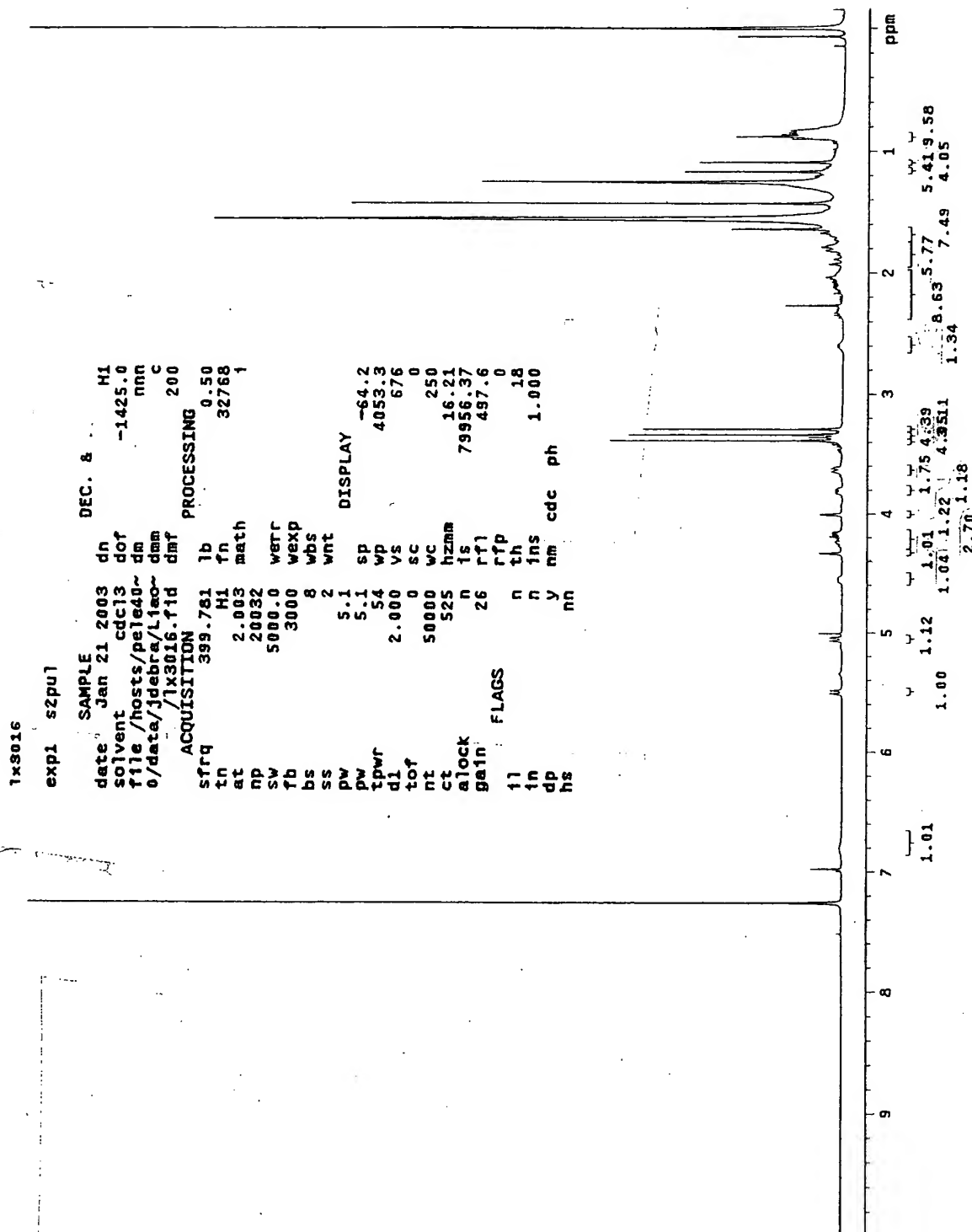


FIG. 62

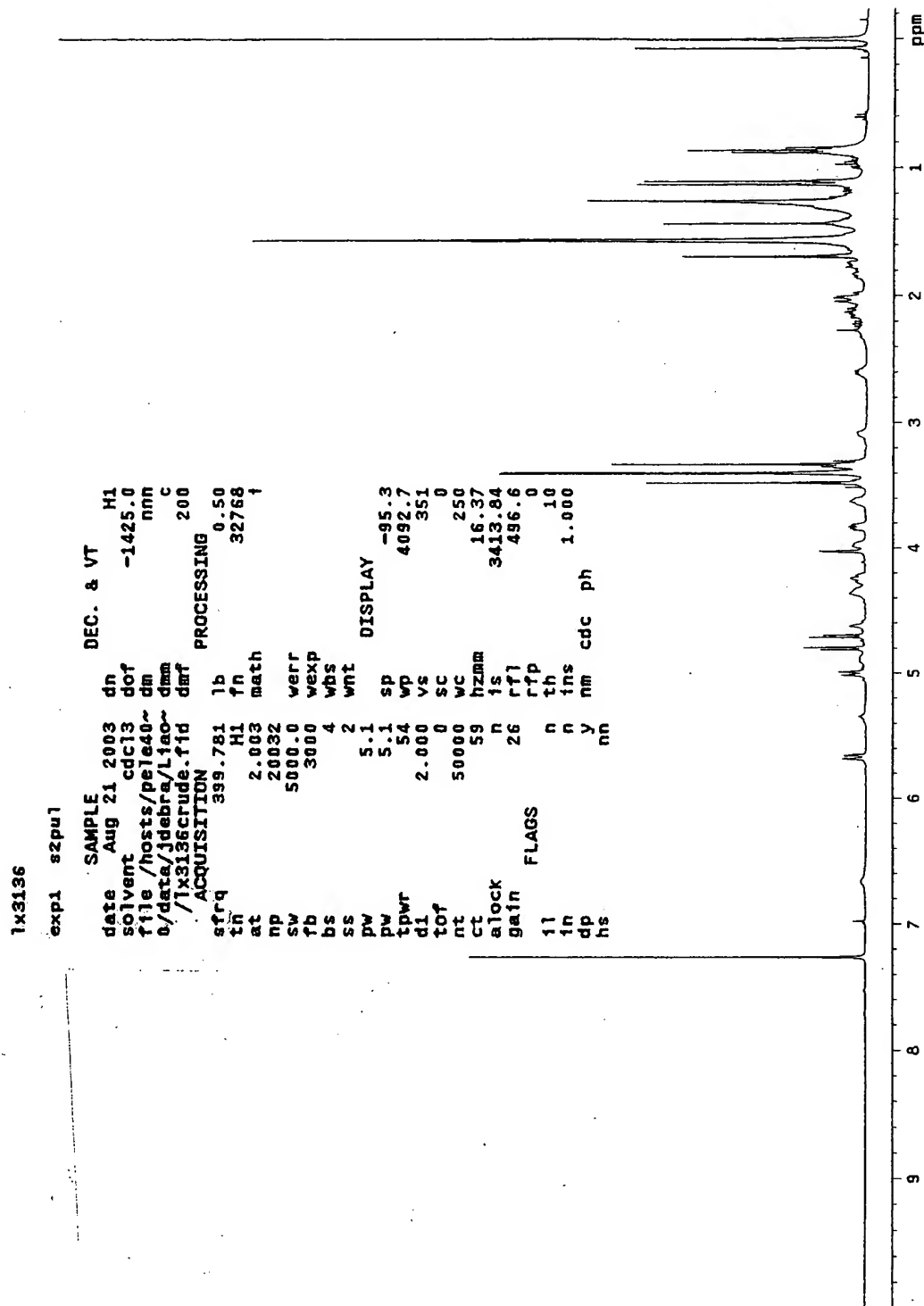


FIG. 63

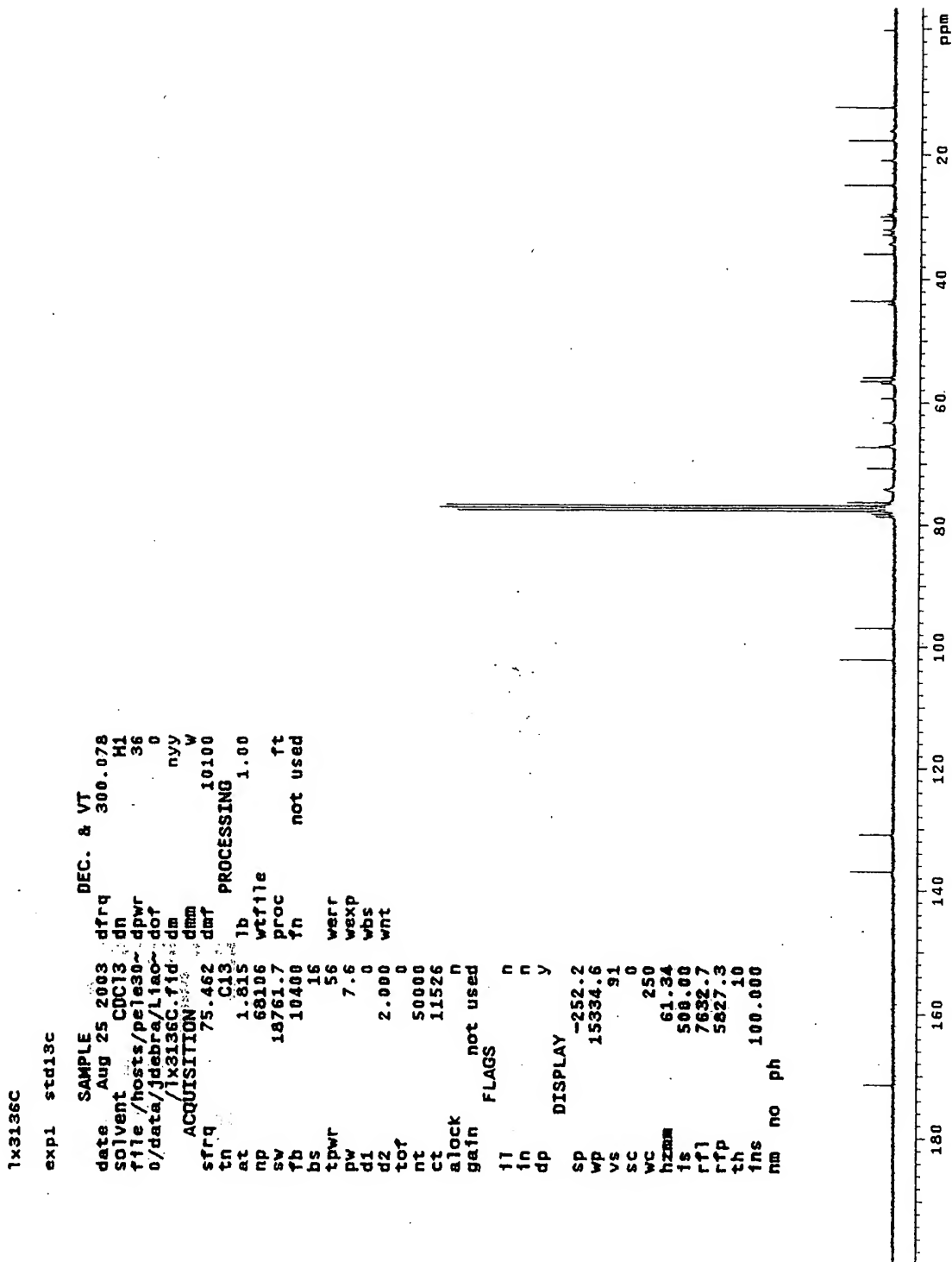


FIG. 64

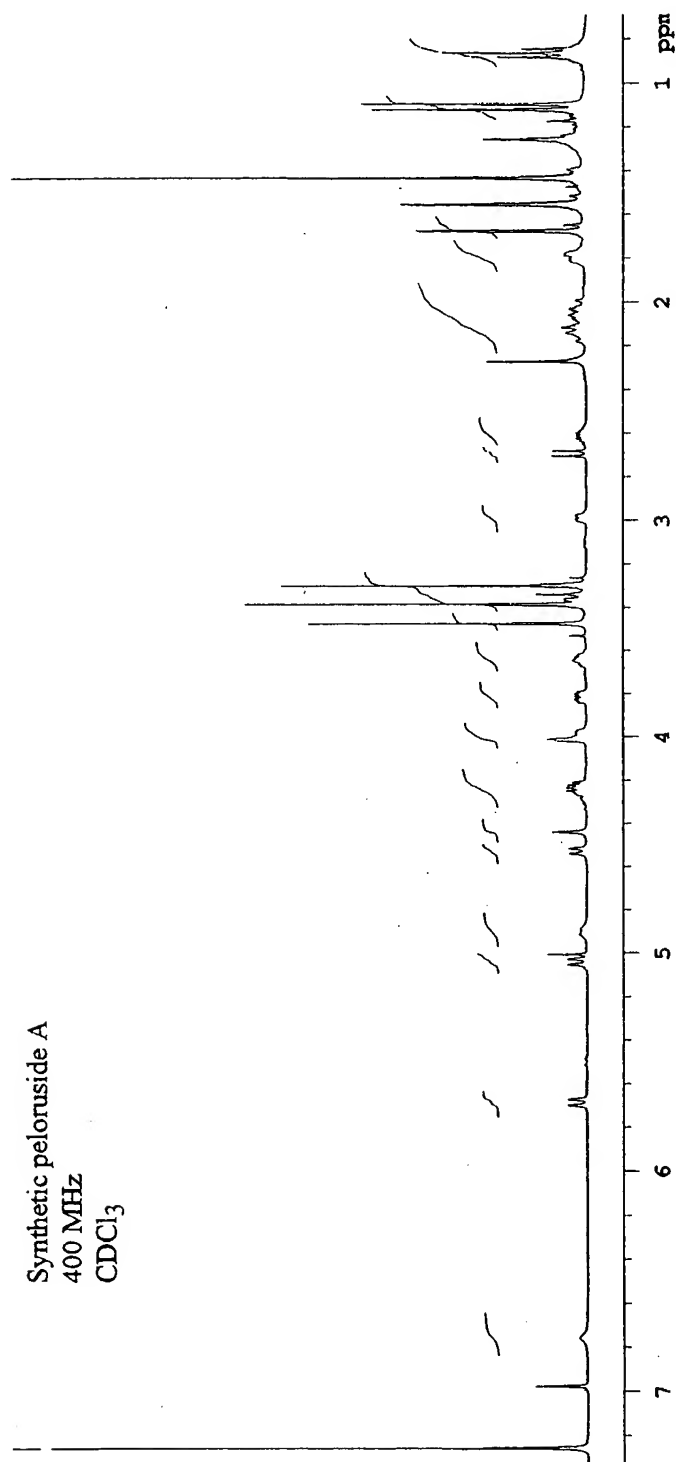


FIG. 65

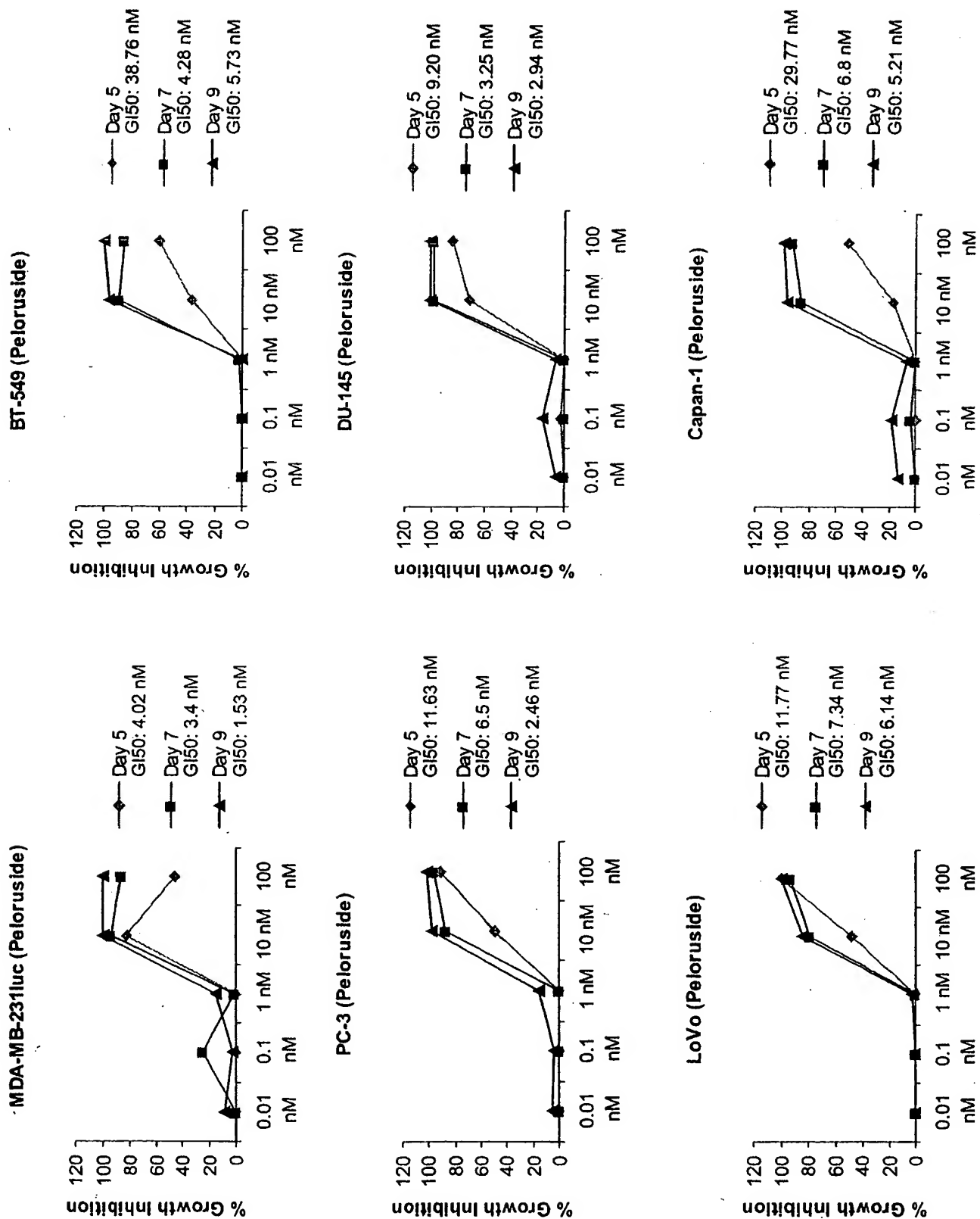


FIG. 66

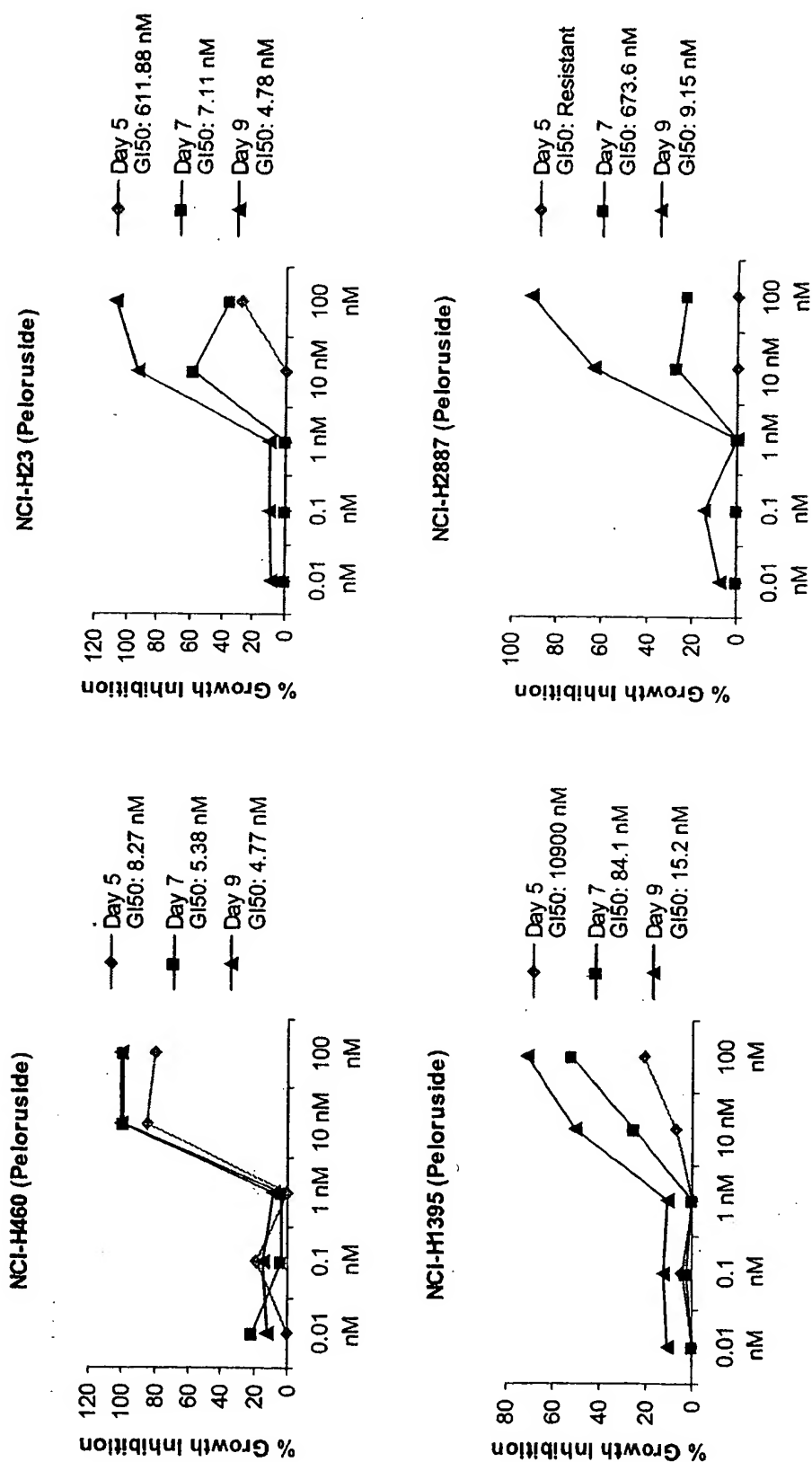


FIG. 67

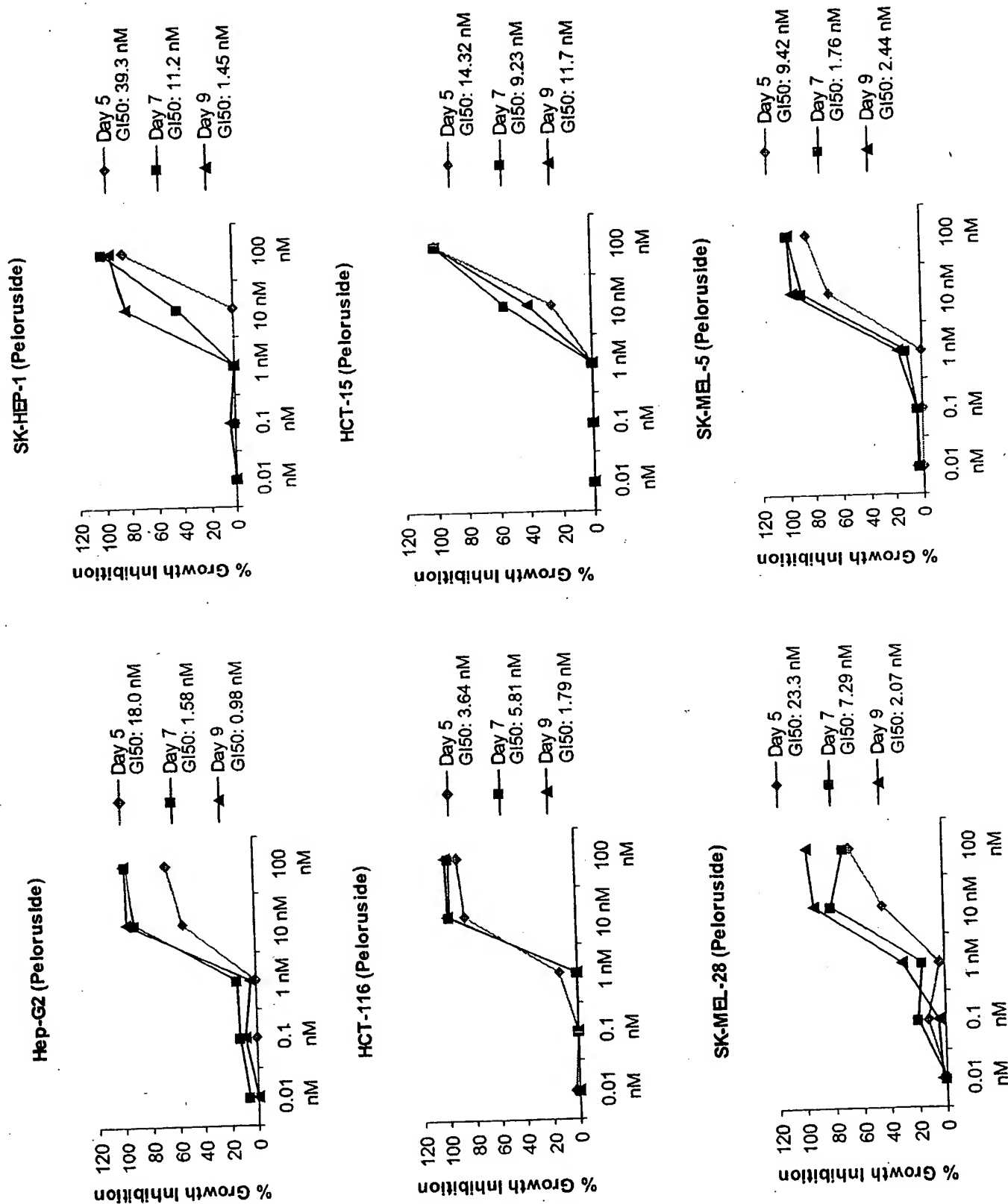


FIG. 68

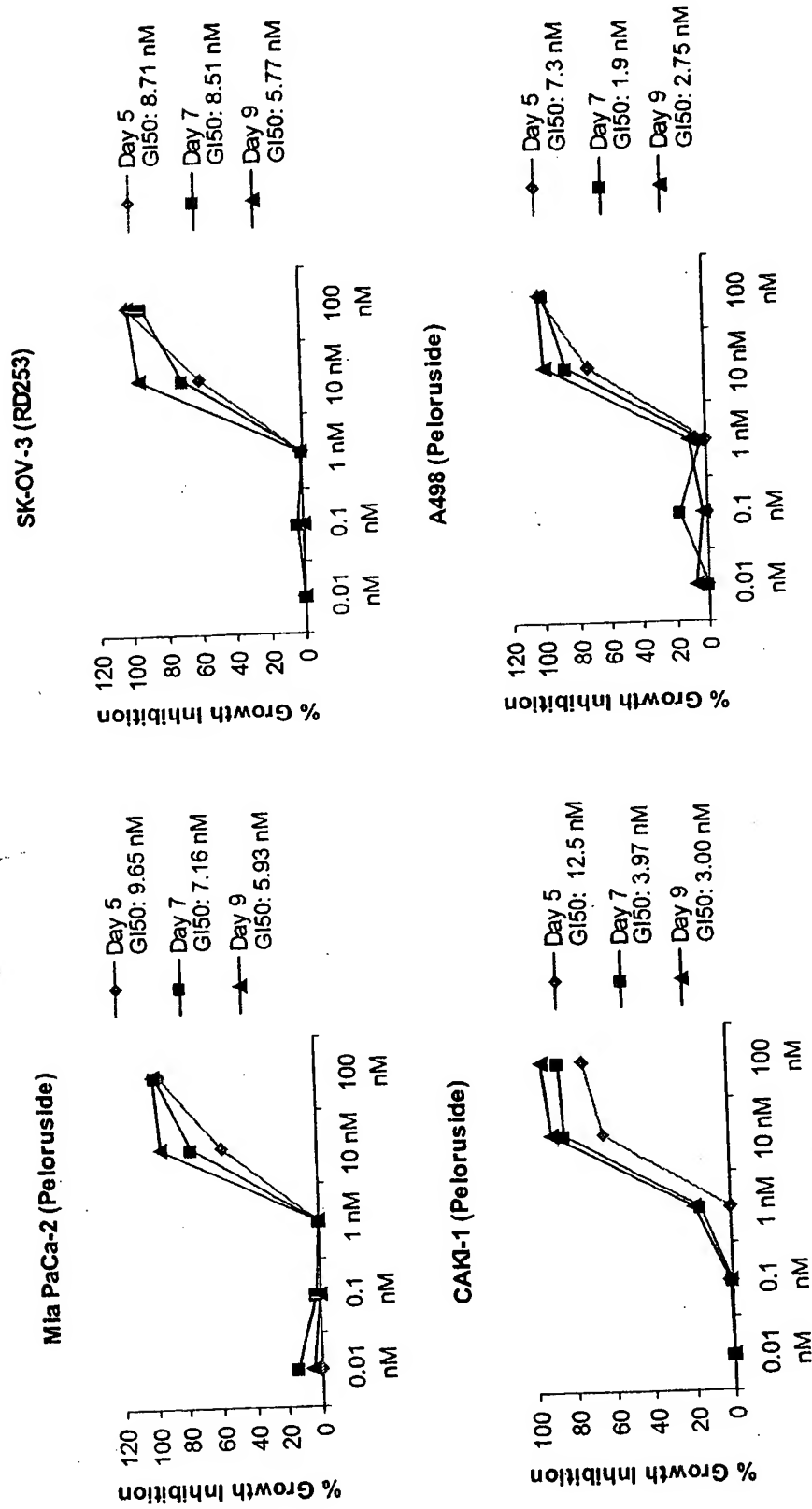


FIG. 69

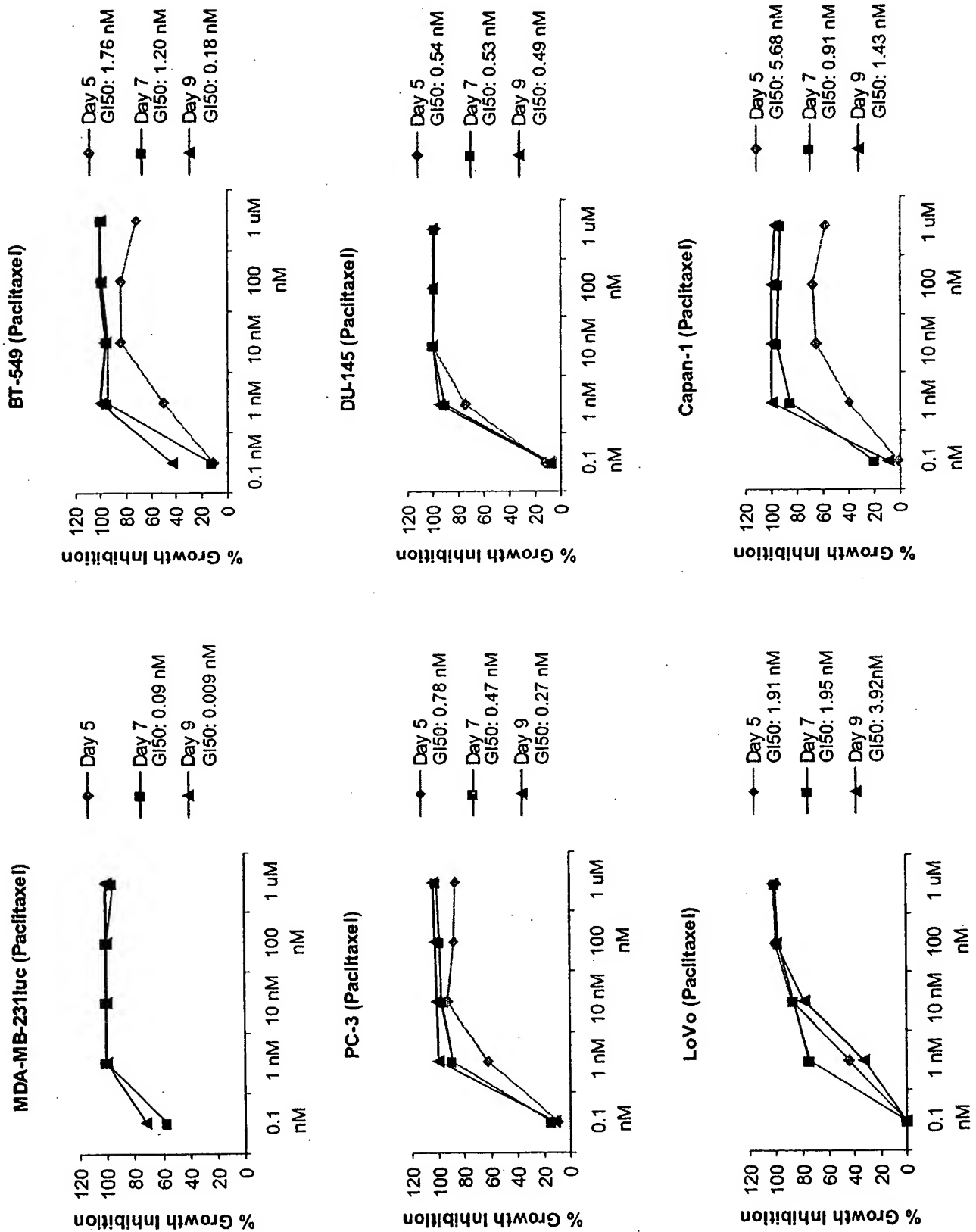


FIG. 70

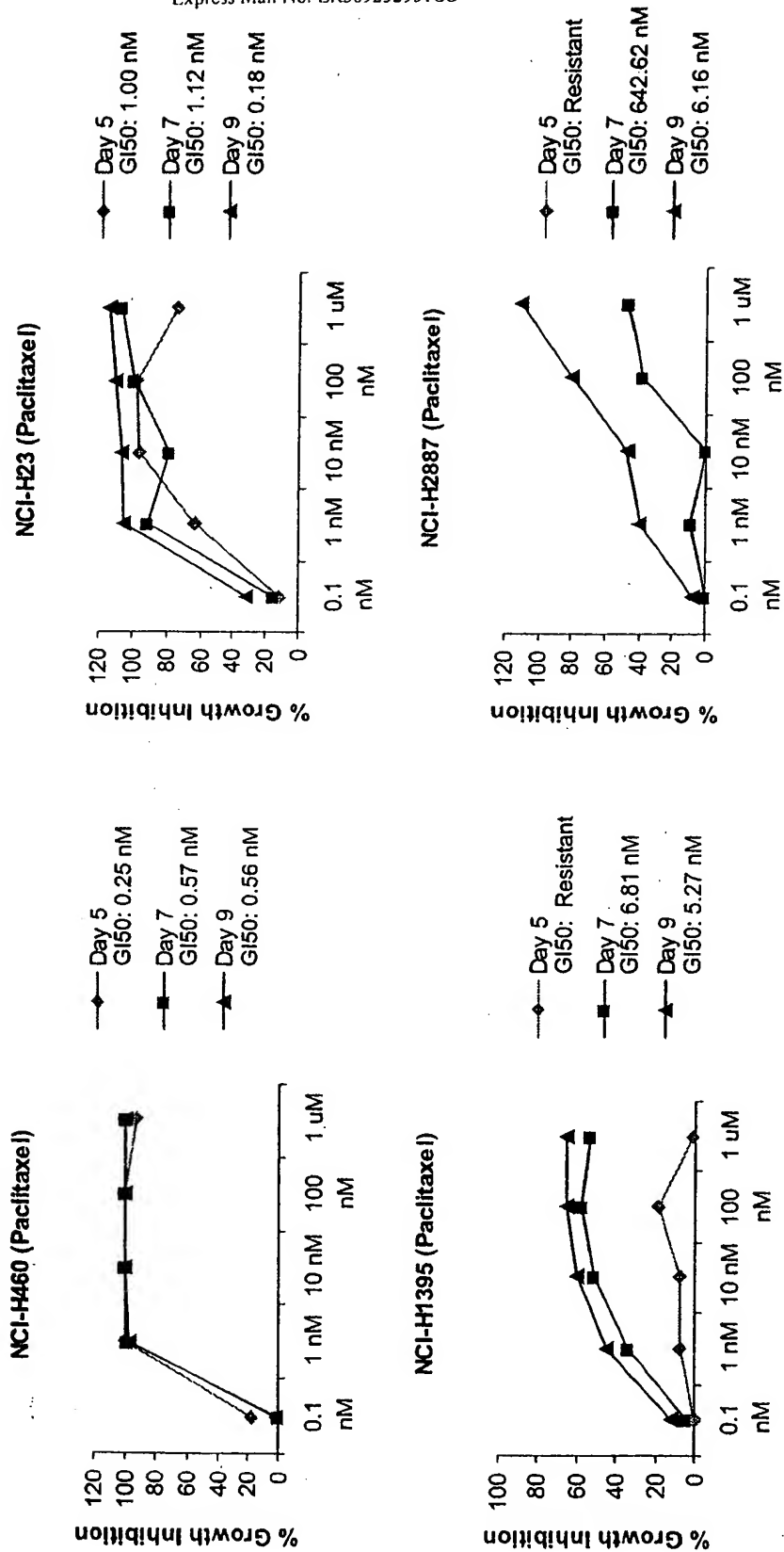


FIG. 71

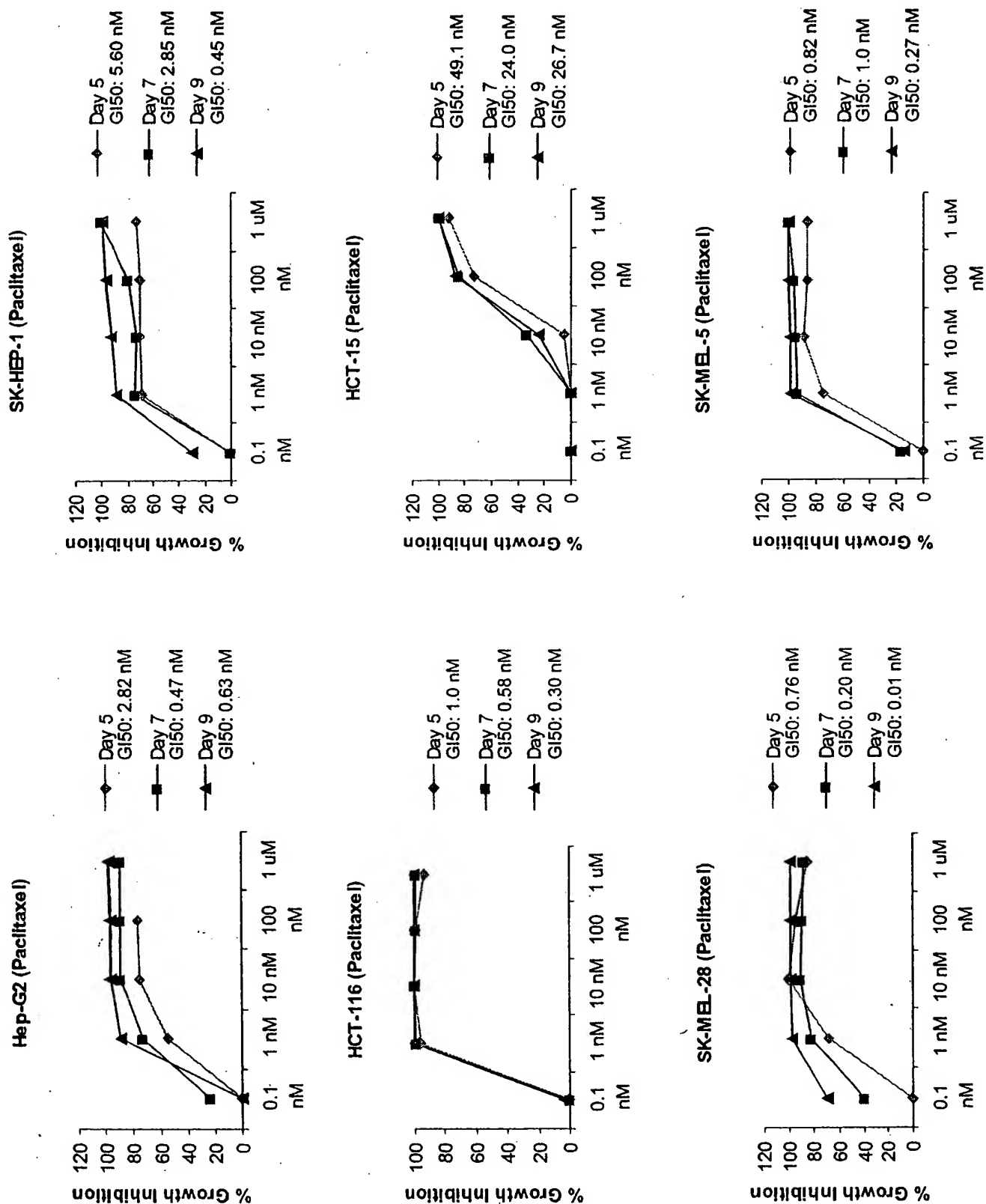


FIG. 72

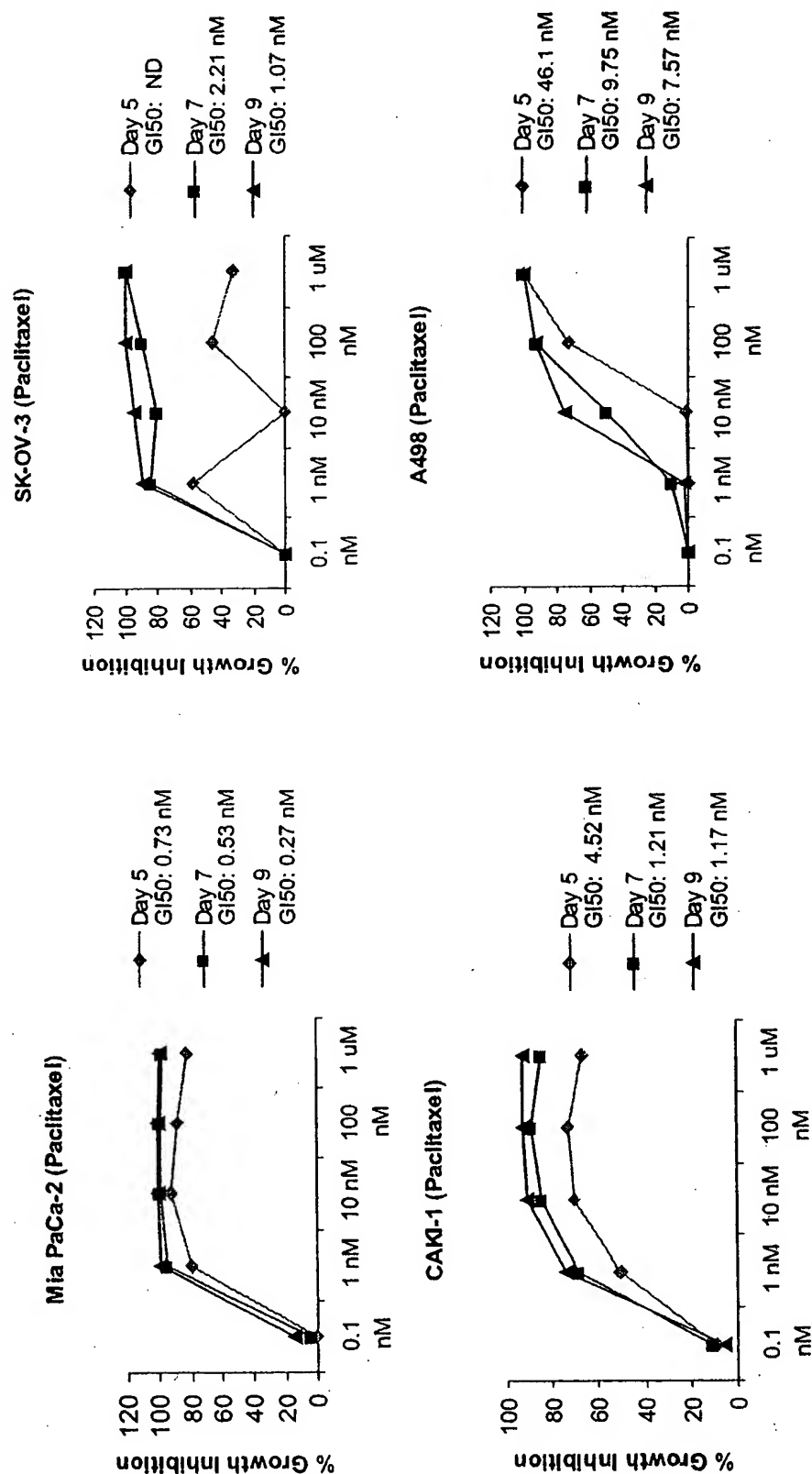


FIG. 73

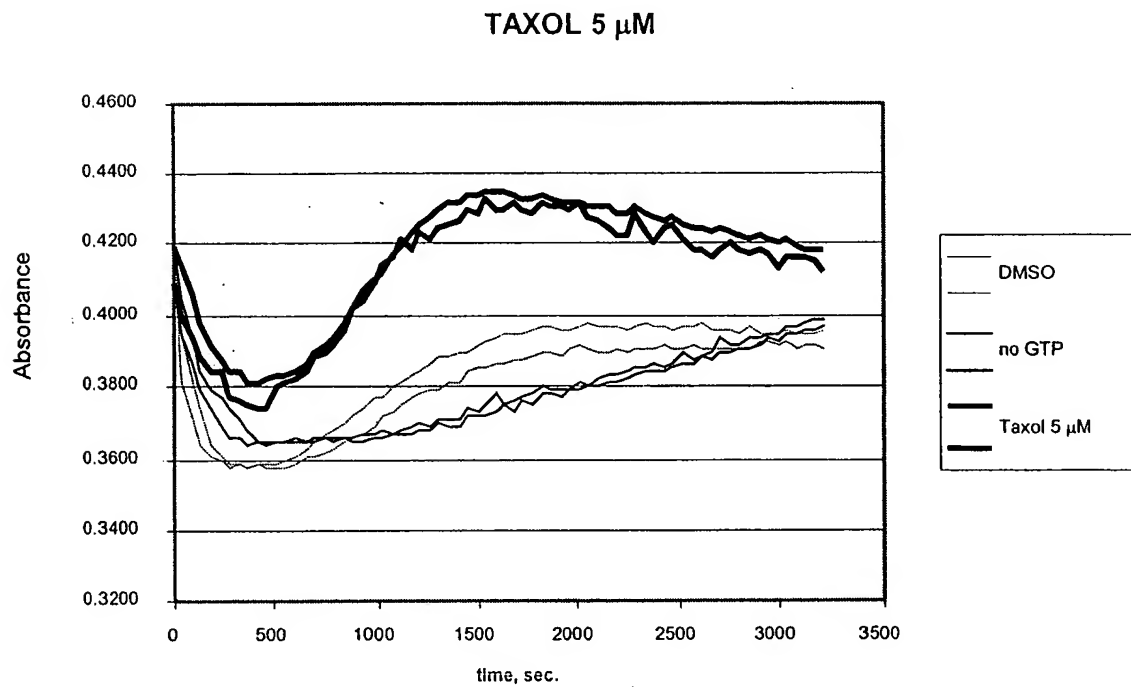
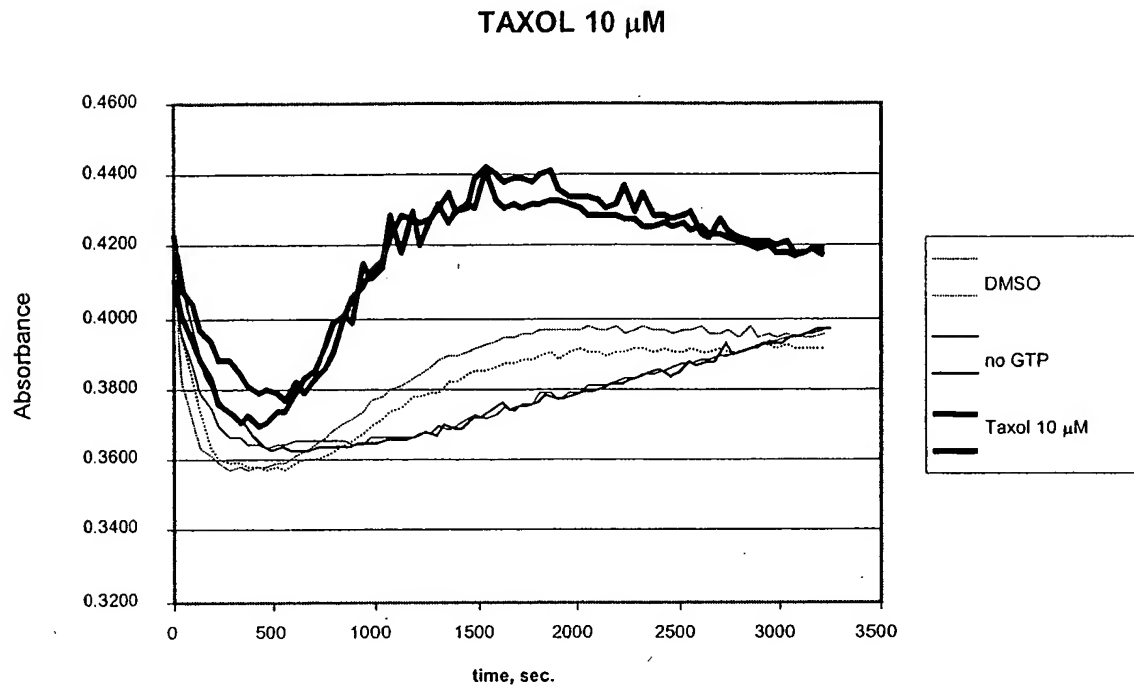
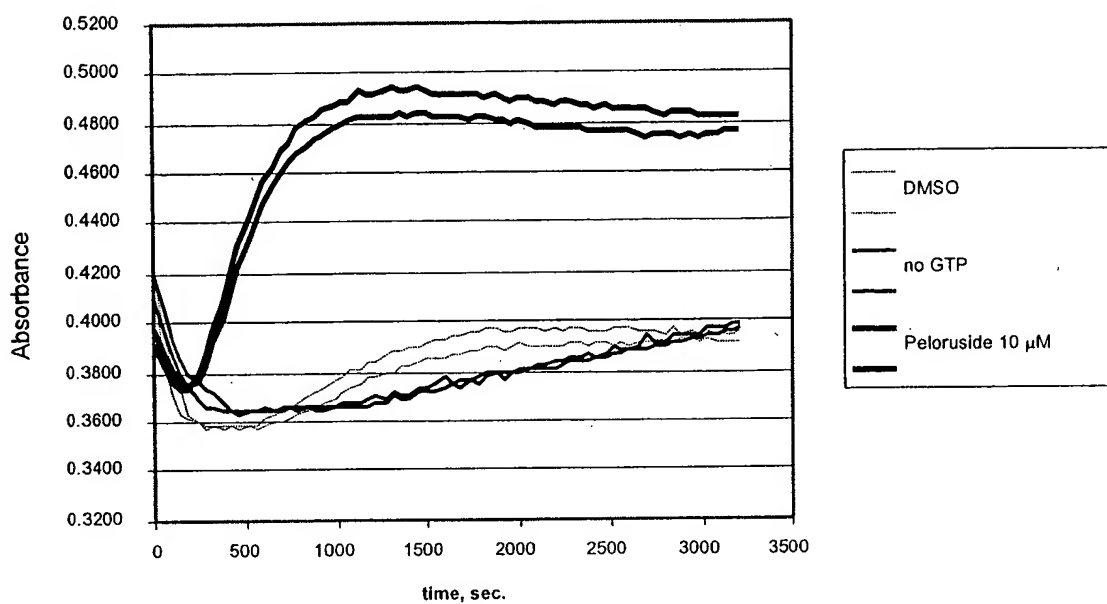


FIG. 74

PELORUSIDE 10 μ M



PELORUSIDE 5 μ M

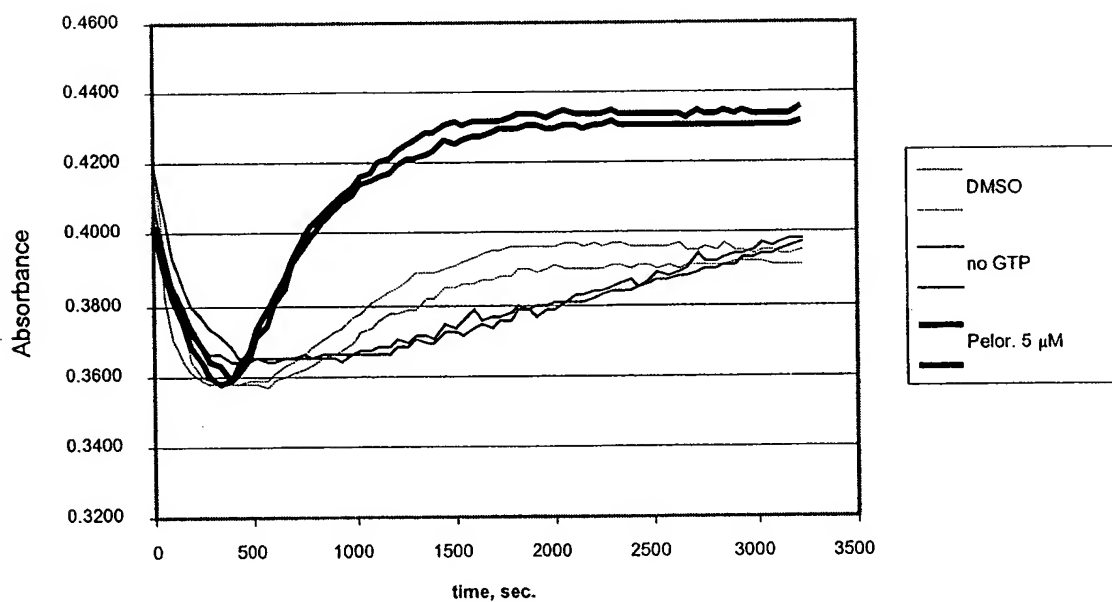
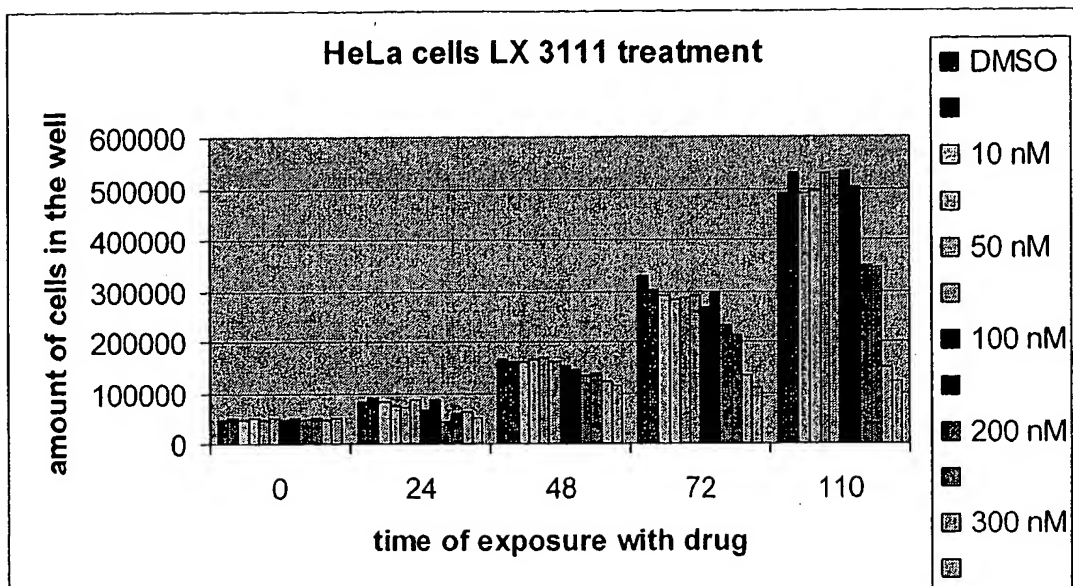


FIG. 75

A



B

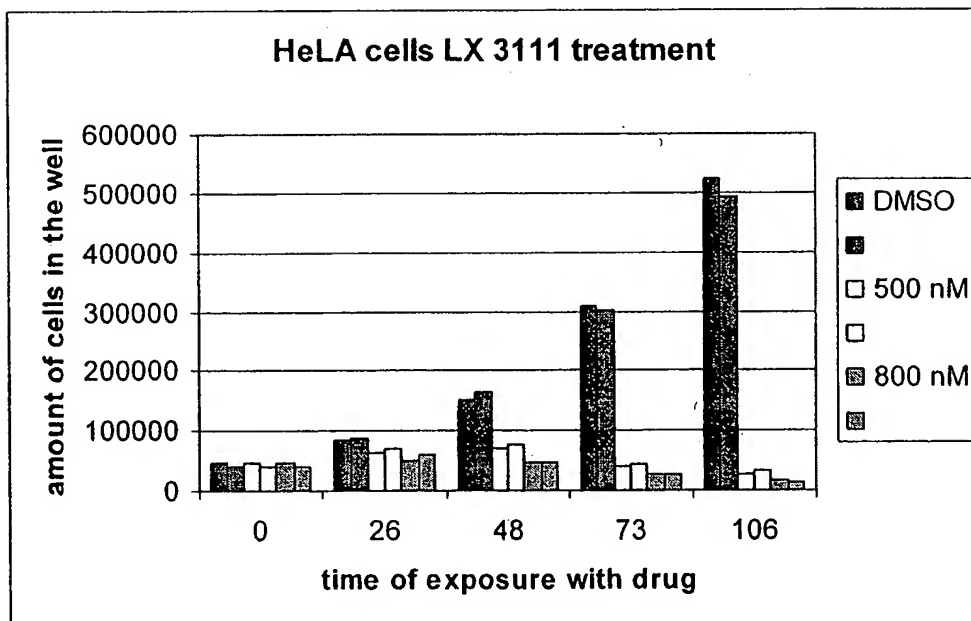


FIG. 76

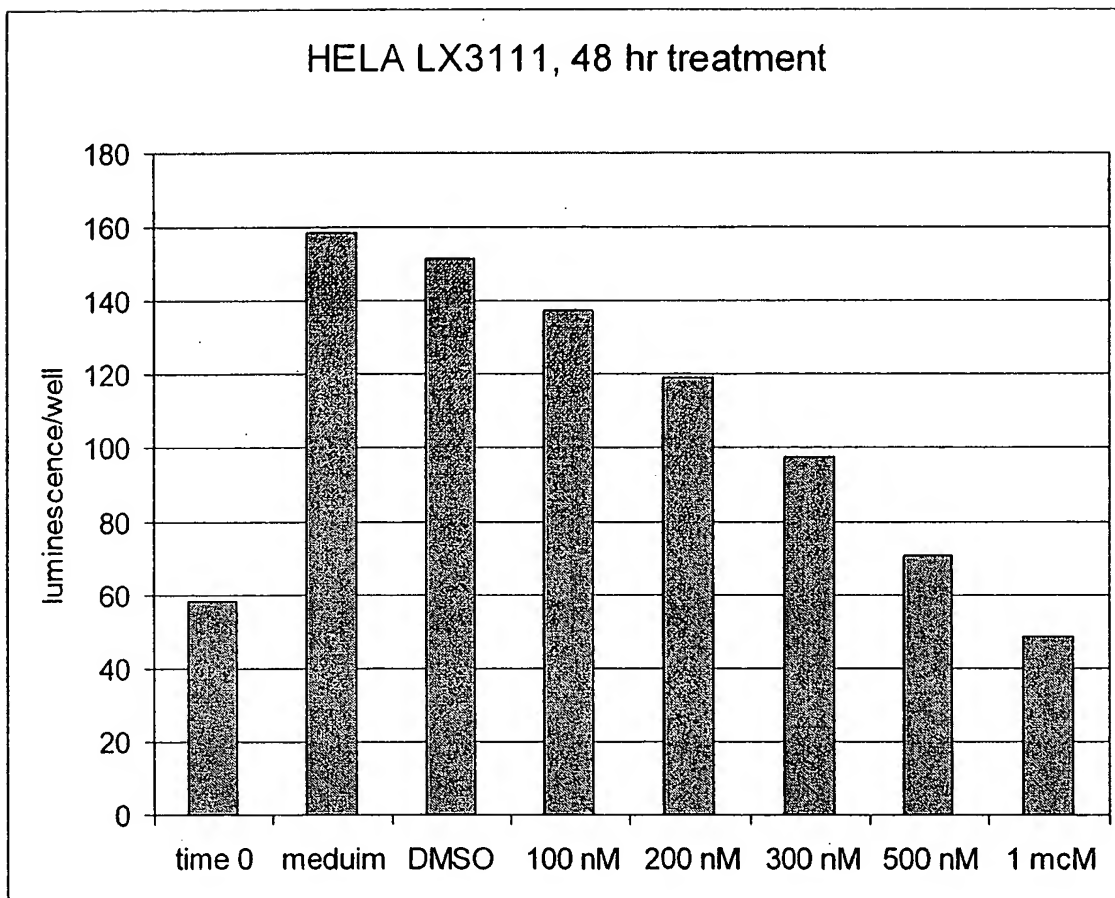
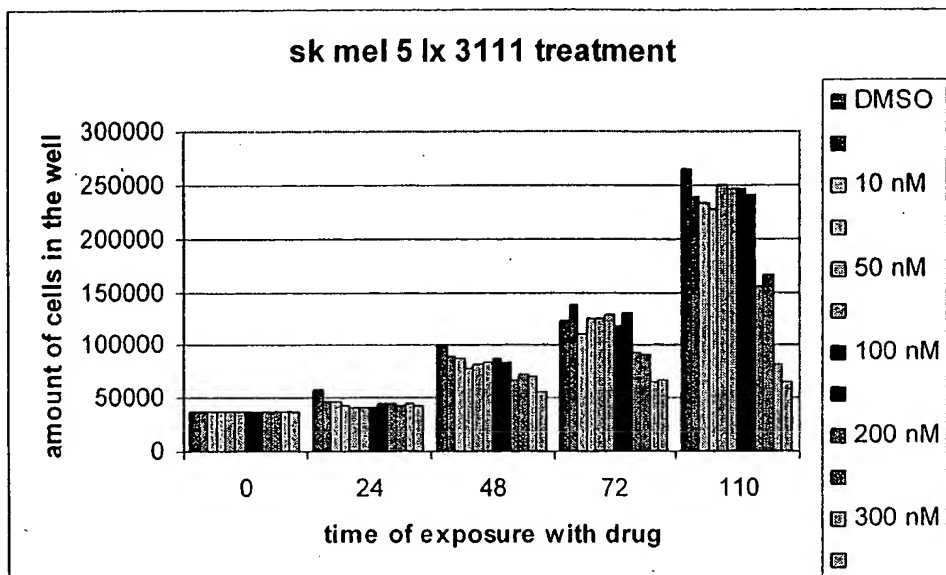


FIG. 77

A



B

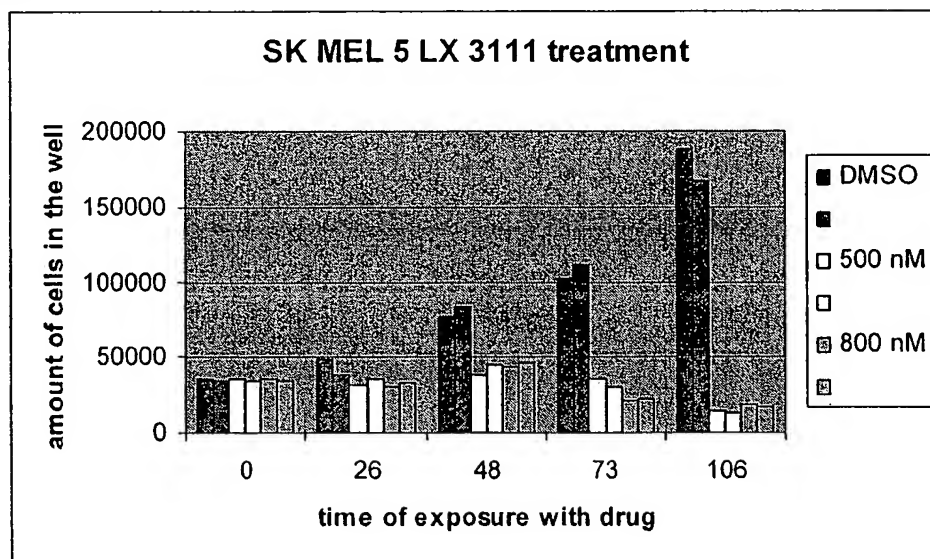


FIG. 78

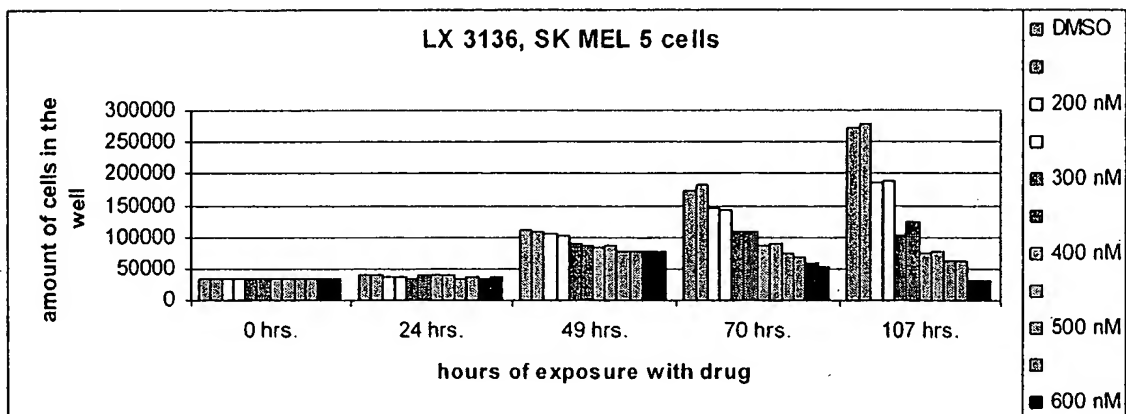


FIG. 79

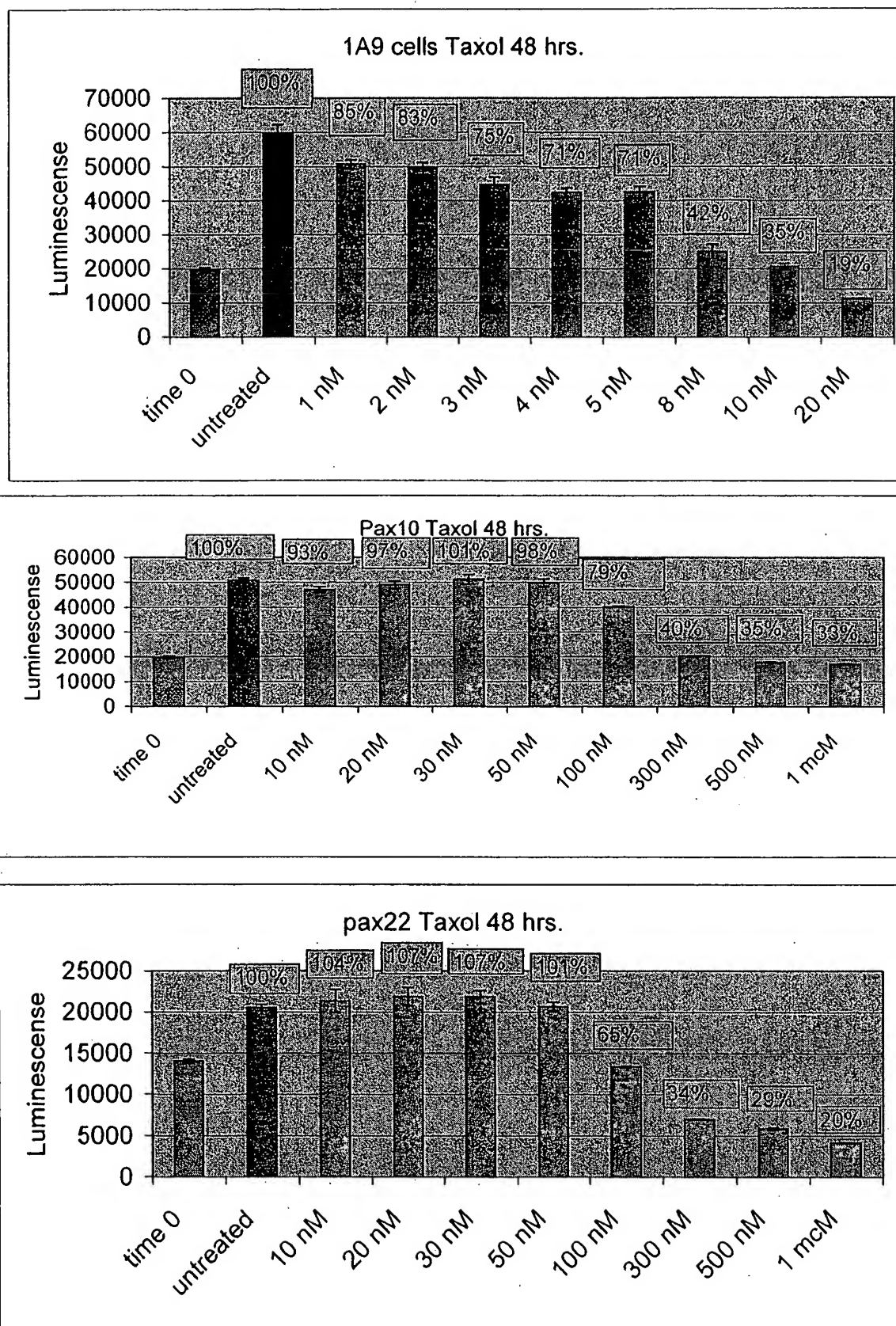


FIG. 80

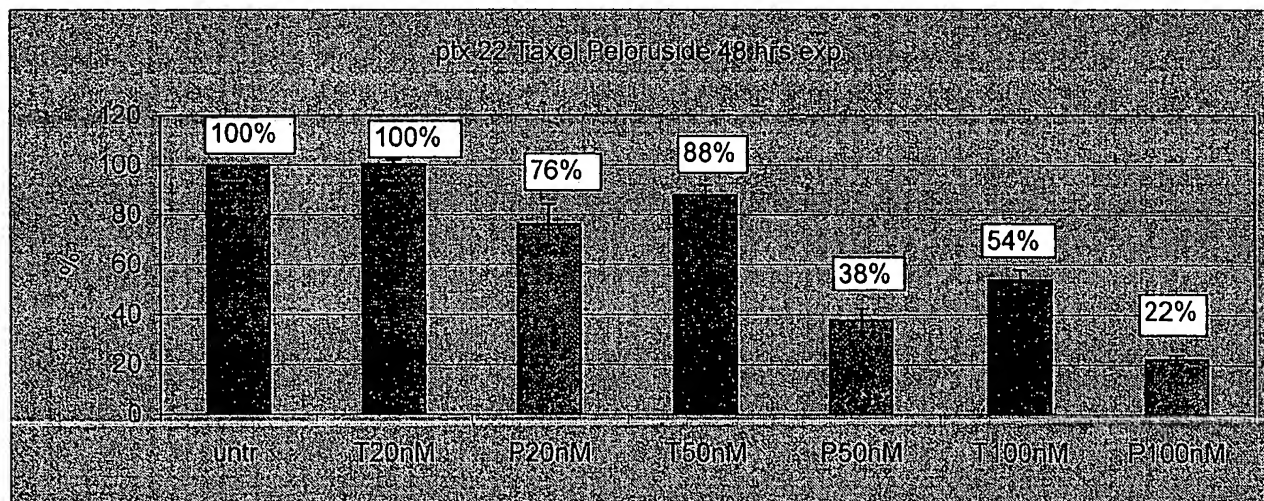
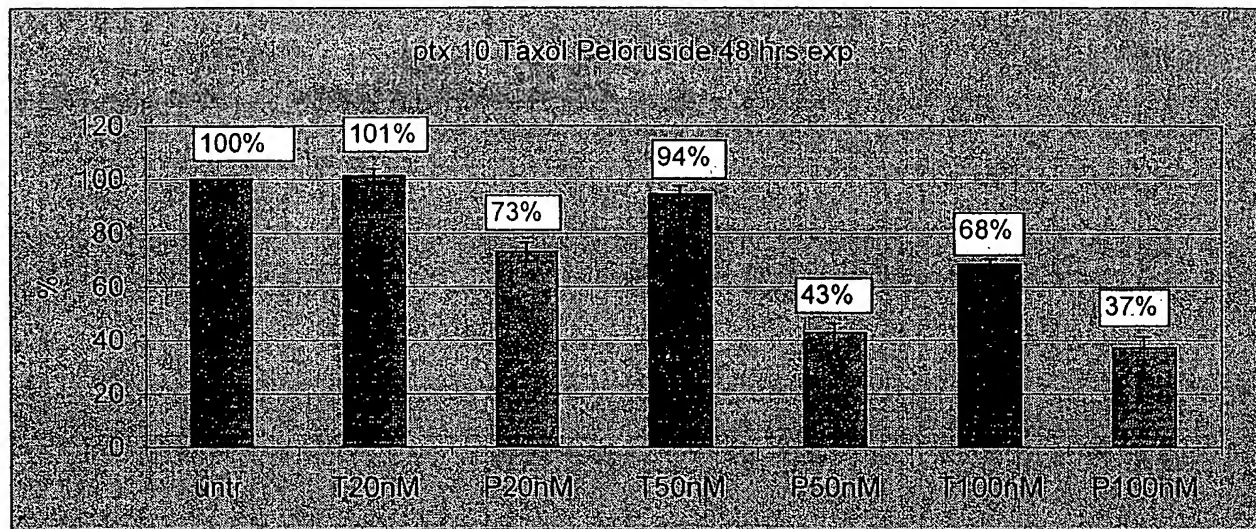
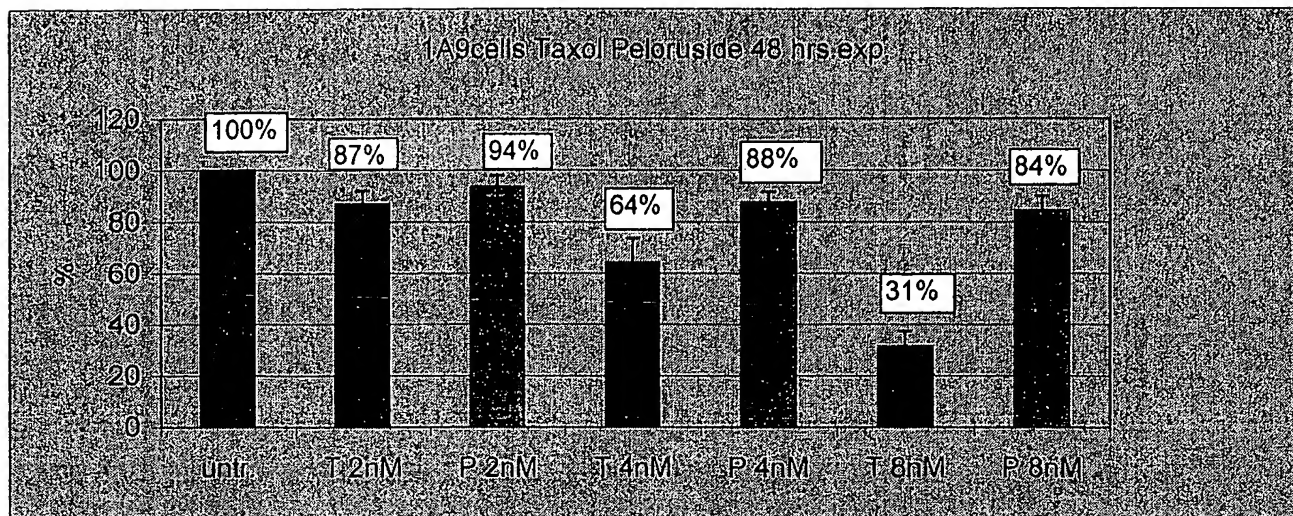


FIG. 81

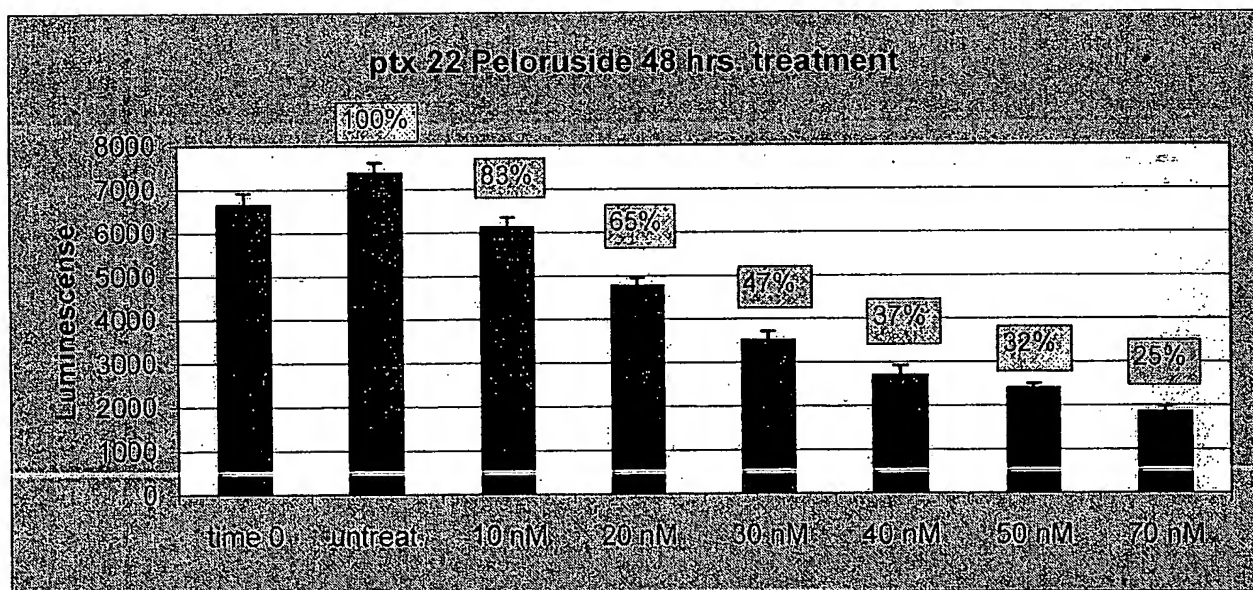
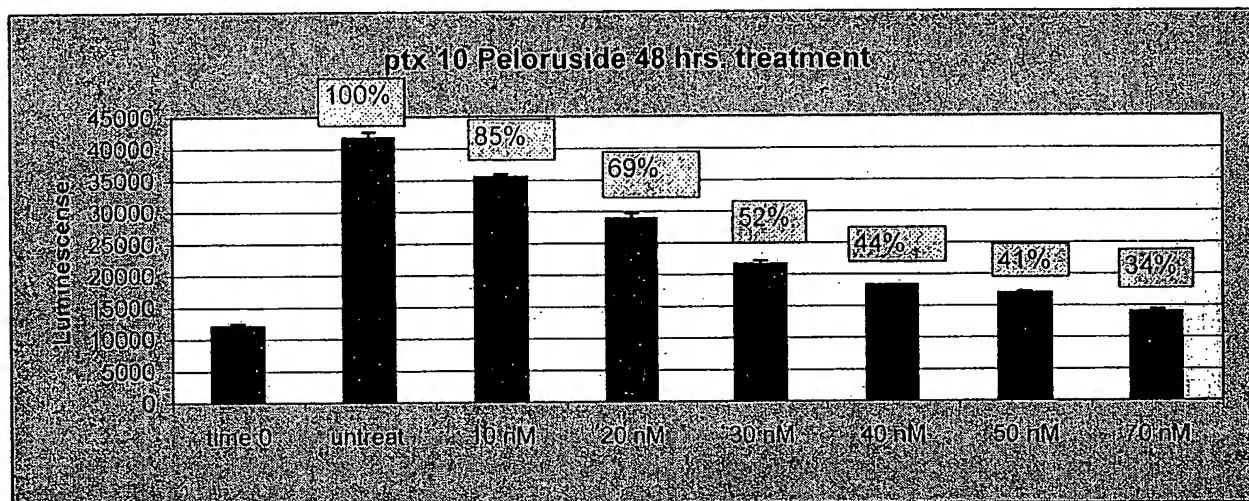
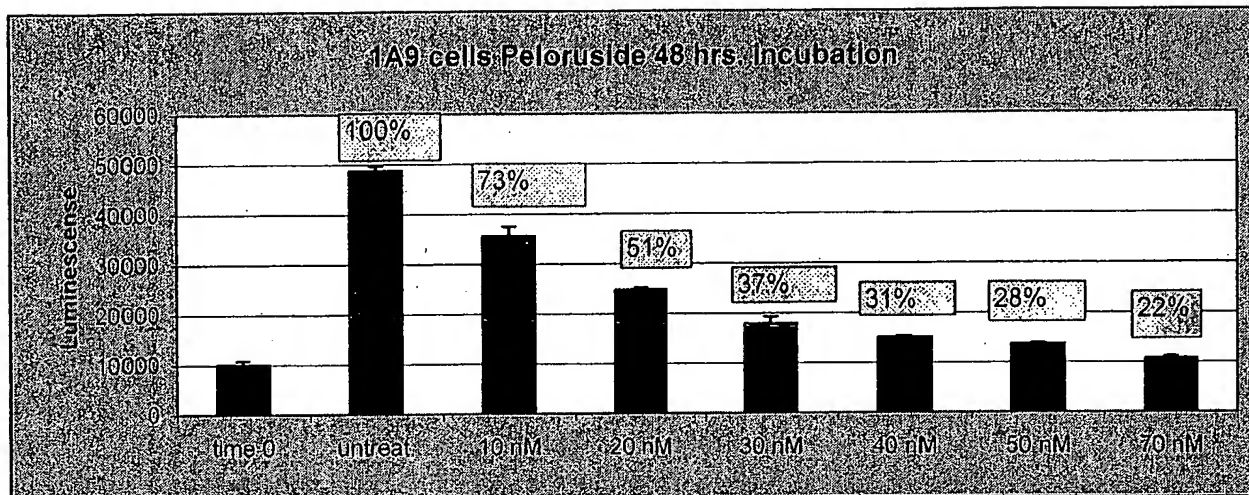


FIG. 82

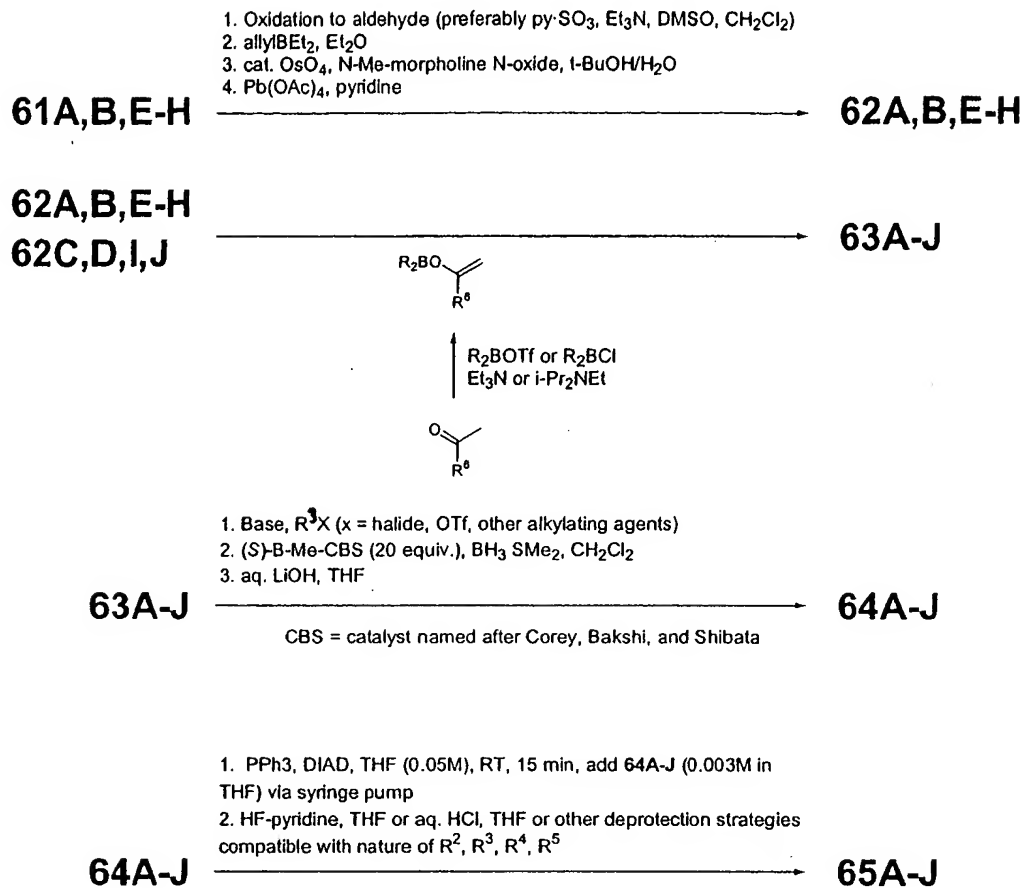
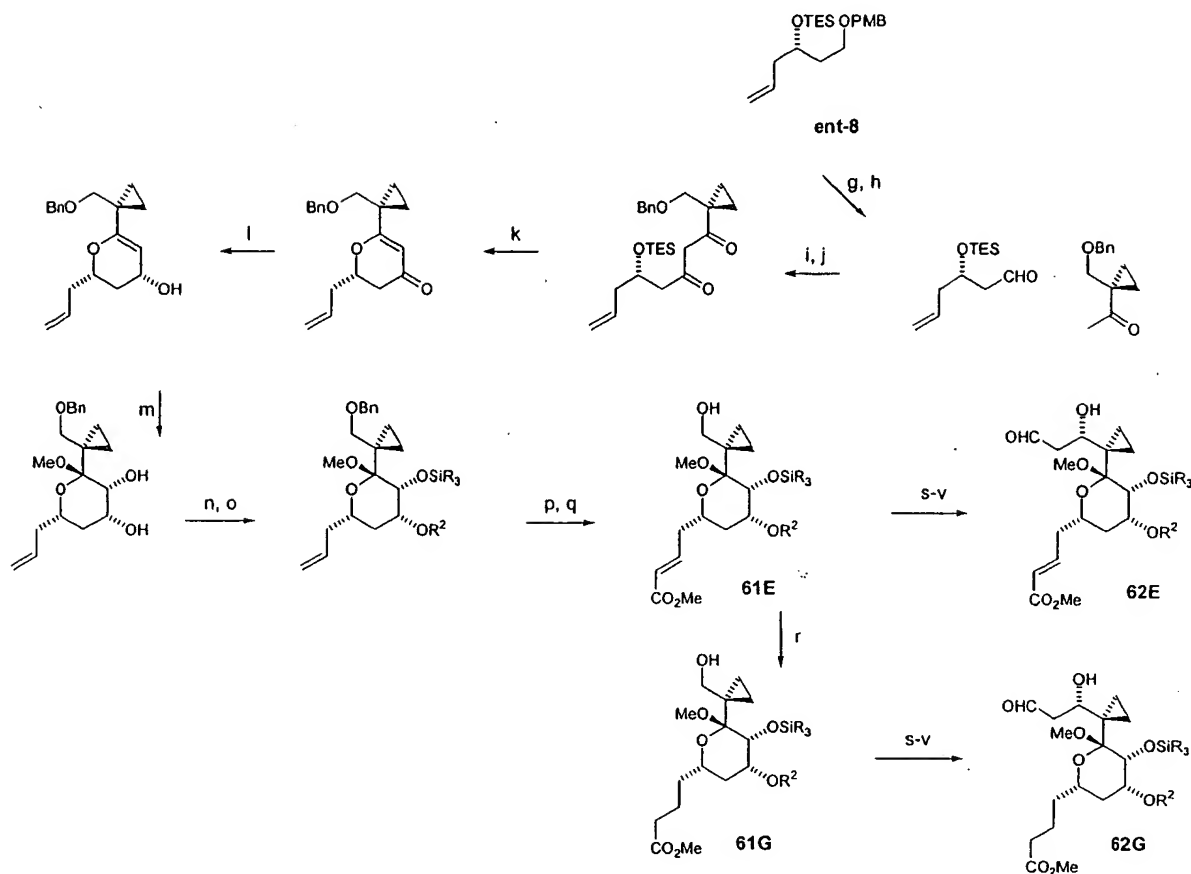
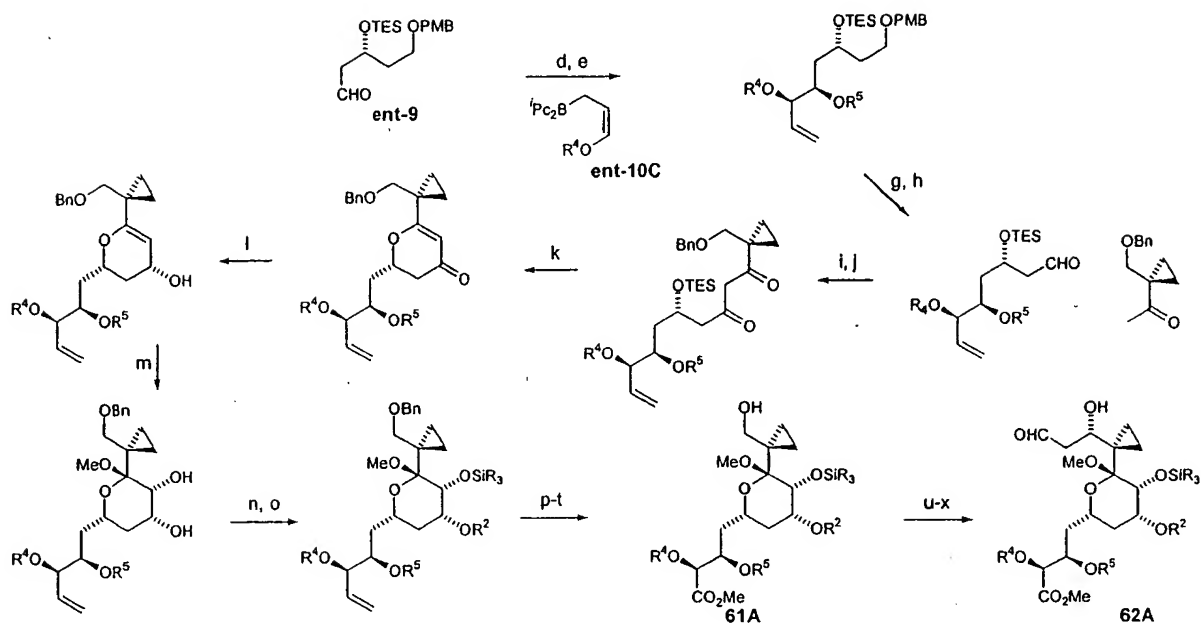


FIG. 83



Reagents and conditions: g) DDQ, CH₂Cl₂/H₂O; h) oxidation to aldehyde; i) LDA, THF, -78°C; j) oxidation to ketone; k) H⁺; l) NaBH₄, CeCl₃·7H₂O, MeOH; m) mCPBA, NaHCO₃, CH₂Cl₂/MeOH; n) base, R₂X; o) R₃SiOTf, 2,6-lutidine; p) LiDBB, THf or Li, naphtalene, THF; q) Ru-alkylidene catalyst (cross metathesis); r) conjugate reduction; s) oxidation to aldehyde; t) allylBEt₂; u) cat. OsO₄, NMO; v) Pb(OAc)₄. PMB = p-methoxybenzyl, TES = triethylsilyl, NMO = 4-methylmorpholine-N-oxide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, LDA = lithium diisopropylamide, mCPBA = m-chloroperbenzoic acid, Bn = benzyl.

FIG. 84

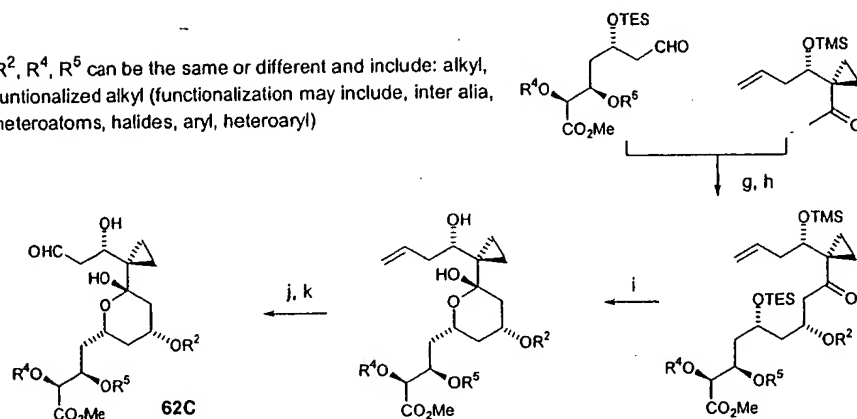


Reagents and conditions: d) ent-10C (prepared from $R^4OCH_2CH=CH_2$, $sBuLi$, THF, $-78^\circ C$, 15 min, then $(-)-lpc_2BOMe$, $-78^\circ C$), then ent-9, $-95^\circ C$, 30% H_2O_2 , NaOH; e) base R_5X ; g) DDQ, CH_2Cl_2/H_2O ; h) oxidation to aldehyde; i) LDA, THF; j) oxidation to ketone; k) H^+ ; l) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; m) mCPBA, $NaHCO_3$, $CH_2Cl_2/MeOH$; n) base, R_2X ; o) TESOTf, 2,6-lutidine, CH_2Cl_2 ; p) cat. OsO_4 , NMO, acetone/ H_2O ; q) $Pb(OAc)_4$, pyridine; r) $NaClO_2$, NaH_2PO_4 , 2-Me-2-butene, $tBuOH/H_2O$; s) CH_2N_2 ; t) hydrogenolysis; u) oxidation to aldehyde; v) allylBET₂; w) cat. OsO_4 , NMO; x) $Pb(OAc)_4$. PMB = p-methoxybenzyl, TES = triethylsilyl, NMO = 4-methylmorpholine-N-oxide, lpc = isopinocampheyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, LDA = lithium diisopropylamide, mCPBA = m-chloroperbenzoic acid, Bn = benzyl.

R^2 , R^4 , R^5 can be the same or different and include: alkyl, functionalized alkyl (functionalization may include, inter alia, heteroatoms, halides, aryl, heteroaryl)

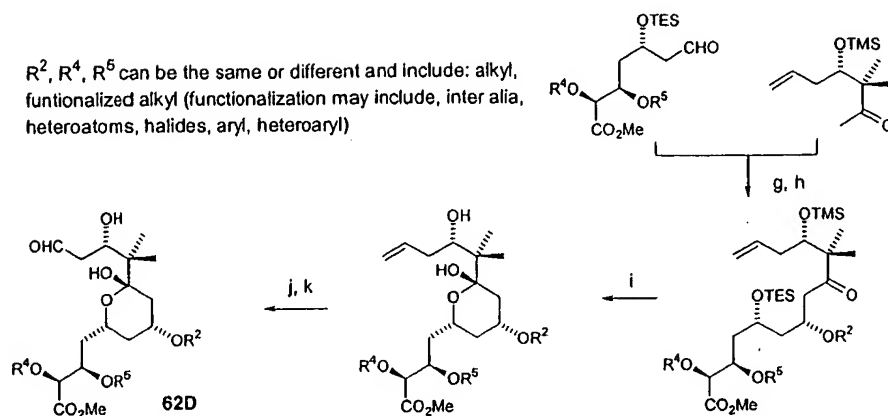
FIG. 85

R^2 , R^4 , R^5 can be the same or different and include: alkyl, functionalized alkyl (functionalization may include, inter alia, heteroatoms, halides, aryl, heteroaryl)



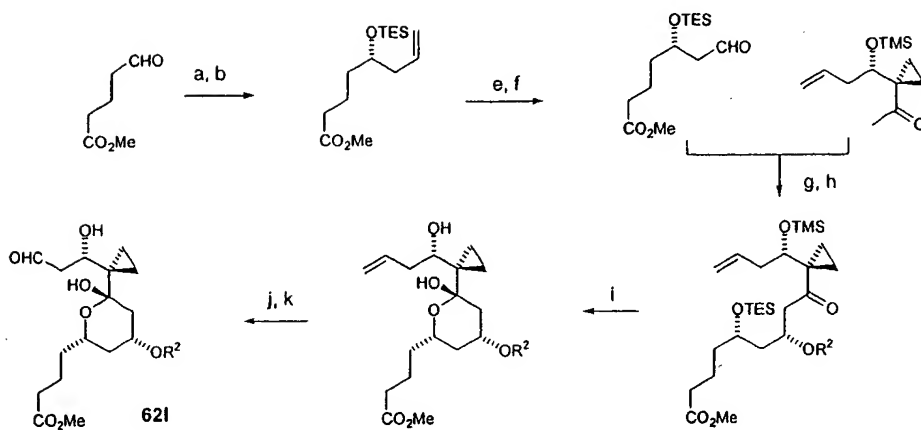
Reagents and conditions: g) LDA, THF; h) base R_5X ; i) H^+ ; j) cat. OsO₄, NMO; k) Pb(OAc)₄. TMS = trimethylsilyl, TES = triethylsilyl, NMO = 4-methylmorpholine-N-oxide, LDA = lithium diisopropylamide.

FIG. 86



Reagents and conditions: g) LDA, THF; h) base R_5X ; i) H^+ ; j) cat. OsO_4 , NMO; k) $Pb(OAc)_4$. TMS = trimethylsilyl, TES = triethylsilyl, NMO = 4-methylmorpholine-N-oxide, LDA = lithium diisopropylamide.

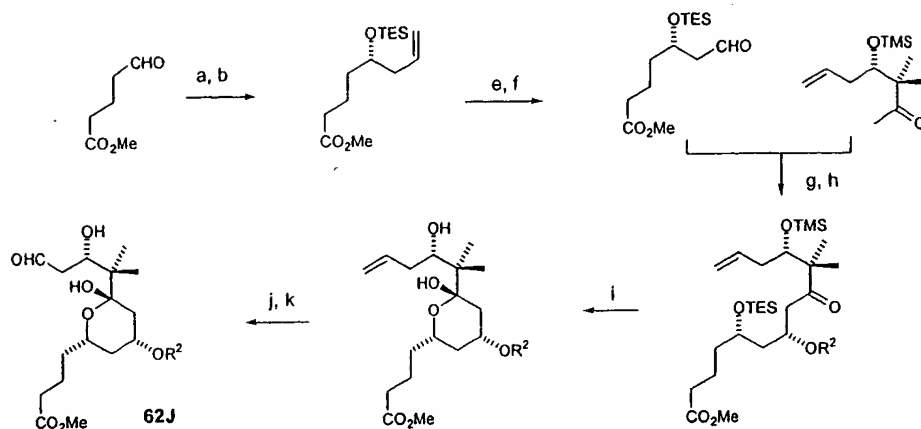
FIG. 87



Reagents and conditions: a) $\text{Ipc}_2\text{Ballyl}$; b) TESCl ; c) cat. OsO_4 , NMO; d) $\text{Pb}(\text{OAc})_4$; e) LDA , THF; f) H^+ ; g) cat. OsO_4 , NMO; h) $\text{Pb}(\text{OAc})_4$. TMS = trimethylsilyl, TES = triethylsilyl, NMO = 4-methylmorpholine-N-oxide, LDA = lithium diisopropylamide.

R^2 can include: alkyl, functionalized alkyl (functionalization may include, inter alia, heteroatoms, halides, aryl, heteroaryl)

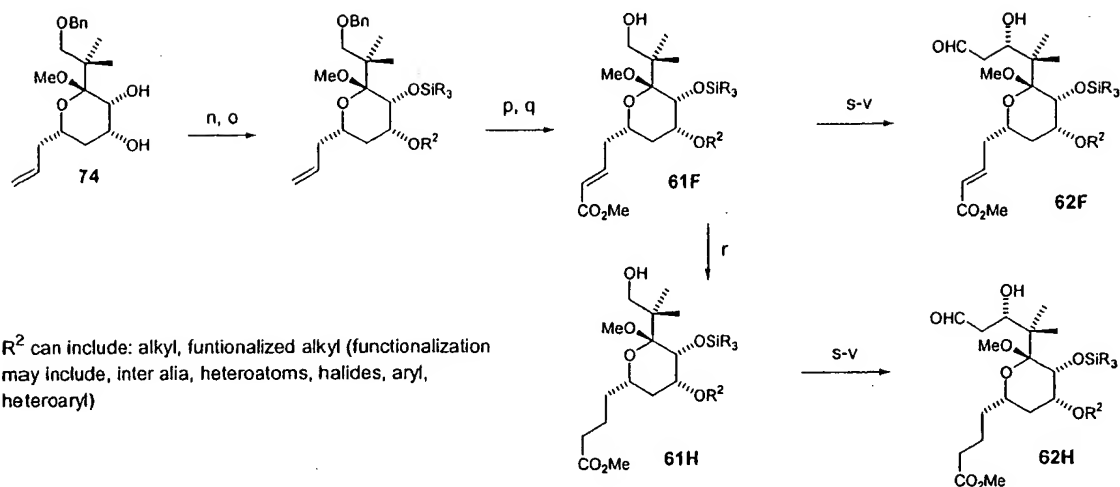
FIG. 88



Reagents and conditions: a) $\text{Ipc}_2\text{Ballyl}$; b) TESCl ; c) cat. OsO_4 , NMO; d) $\text{Pb}(\text{OAc})_4$; e) base R_5X ; f) H^+ ; g) cat. OsO_4 , NMO; h) $\text{Pb}(\text{OAc})_4$. TMS = trimethylsilyl, TES = triethylsilyl, NMO = 4-methylmorpholine-N-oxide, LDA = lithium diisopropylamide.

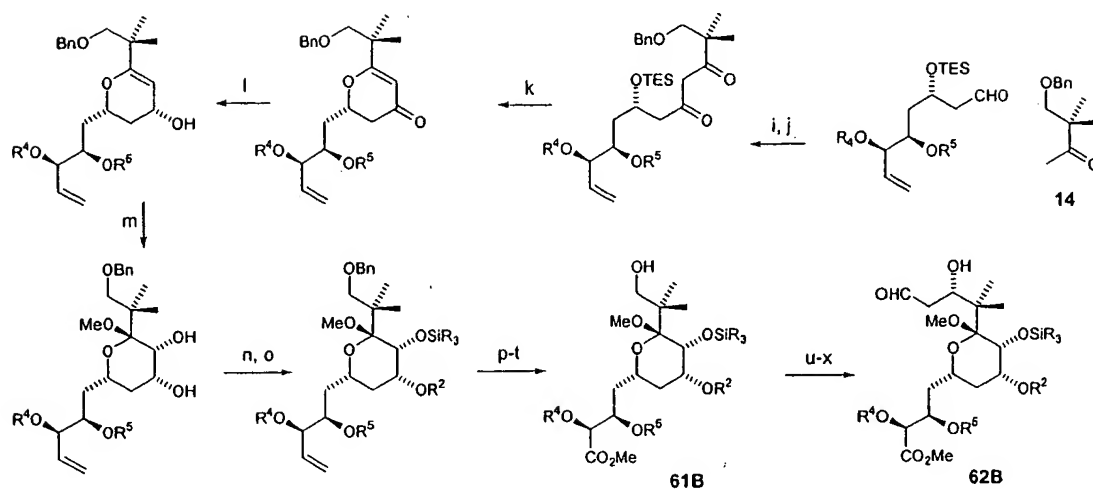
R^2 can include: alkyl, functionalized alkyl (functionalization may include, inter alia, heteroatoms, halides, aryl, heteroaryl)

FIG. 89



Reagents and conditions: *n*) base, R_2X ; *o*) TESOTf, 2,6-lutidine; *p*) LiDBB, THf or Li, naphtalene, THF; *q*) Ru-alkylidene catalyst (cross metathesis); *r*) conjugate reduction; *s*) oxidation to aldehyde; *t*) allylBET₂; *u*) cat. OsO₄, NMO; *v*) Pb(OAc)₄ PMB = p-methoxybenzyl, TES = triethylsilyl, NMO = 4-methylmorpholine-N-oxide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, LDA = lithium diisopropylamide, mCPBA = m-chloroperbenzoic acid, Bn = benzyl.

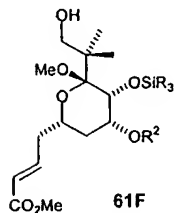
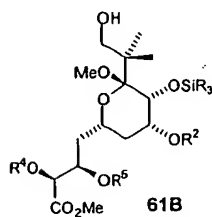
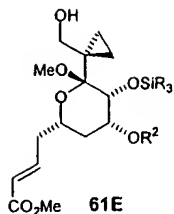
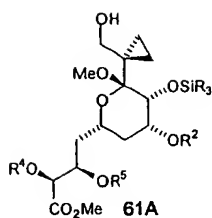
FIG. 90



Reagents and conditions: i) LDA, THF; j) oxidation to ketone; k) H^+ ; l) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; m) mCPBA, $NaHCO_3$, $CH_2Cl_2/MeOH$; n) base, R_2X ; o) TESOTf, 2,6-lutidine, CH_2Cl_2 ; p) cat. OsO_4 , NMO, acetone/ H_2O ; q) $Pb(OAc)_4$, pyridine; r) $NaClO_2$, NaH_2PO_4 , 2-Me-2-butene, $tBuOH/H_2O$; s) CH_2N_2 ; t) hydrogenolysis; u) oxidation to aldehyde; v) allyl BEt_2 ; w) cat. OsO_4 , NMO; x) $Pb(OAc)_4$. PMB = p-methoxybenzyl, TES = triethylsilyl, NMO = 4-methylmorpholine-N-oxide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, LDA = lithium diisopropylamide, mCPBA = m-chloroperbenzoic acid, Bn = benzyl.

R^2 , R^4 , R^5 can be the same or different and include: alkyl, functionalized alkyl (functionalization may include, inter alia, heteroatoms, halides, aryl, heteroaryl)

FIG. 91



R^2 , R^4 , R^5 can be the same or different and include: alkyl,
 functionalized alkyl (functionalization may include, inter alia,
 heteroatoms, halides, aryl, heteroaryl)

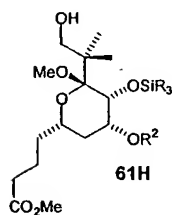
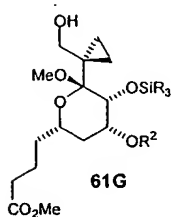
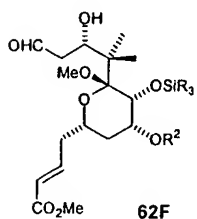
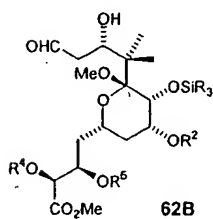
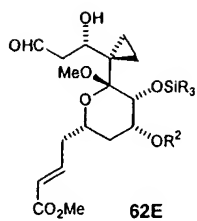
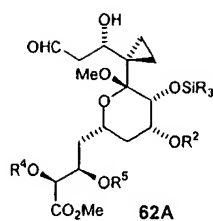


FIG. 92



R^2 , R^4 , R^5 can be the same or different and include: alkyl,
 functionalized alkyl (functionalization may include, inter alia,
 heteroatoms, halides, aryl, heteroaryl)

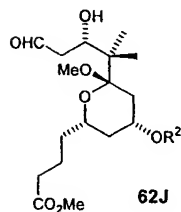
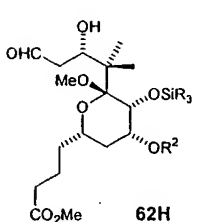
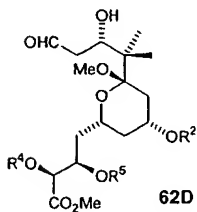
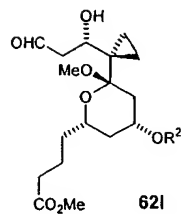
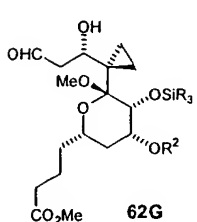
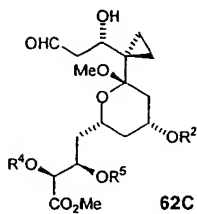
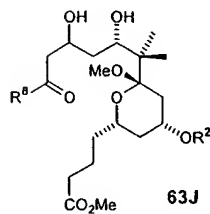
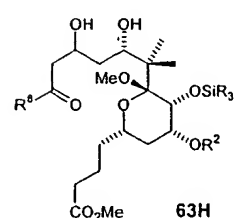
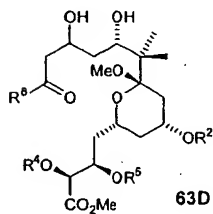
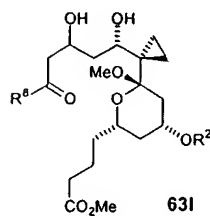
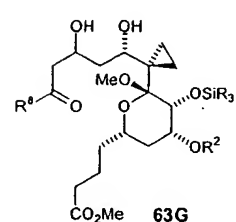
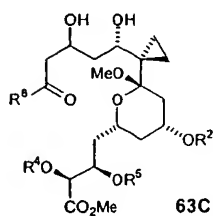
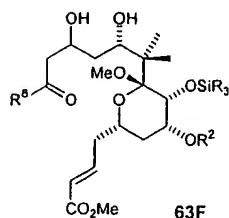
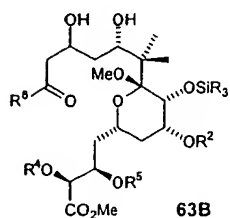
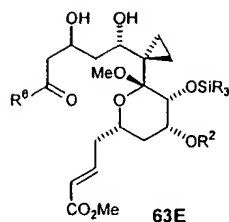
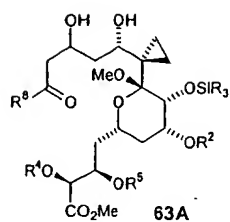
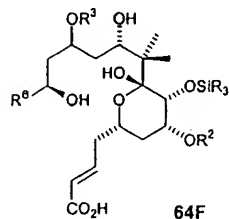
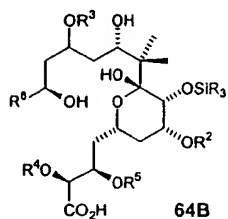
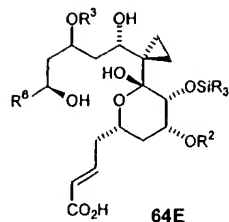
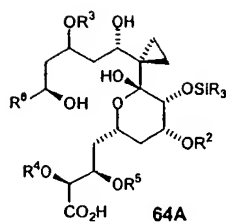


FIG. 93



R^2 , R^4 , R^5 can be the same or different and include: alkyl, functionalized alkyl (functionalization may include, inter alia, heteroatoms, halides, aryl, heteroaryl), and where R^8 = aryl, heteroaryl, alkyl, functionalized alkyl, alkenyl, functionalized alkenyl, alkynyl, functionalized alkynyl (functionalization may include, inter alia, heteroatoms, halides, aryl, heteroaryl).

FIG. 94



R^2, R^3, R^4, R^5 can be the same or different and include:
 alkyl, functionalized alkyl (functionalization may include,
 inter alia, heteroatoms, halides, aryl, heteroaryl), and
 where $R^8 =$ aryl, heteroaryl, alkyl, functionalized alkyl,
 alkenyl, functionalized alkenyl, alkynyl, functionalized
 alkynyl (functionalization may include, inter alia,
 heteroatoms, halides, aryl, heteroaryl). The configuration
 at the carbon bearing the OR^3 substituent can have the *R*-
 or *S*-configuration

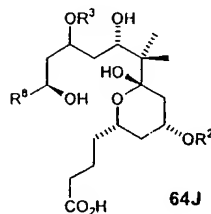
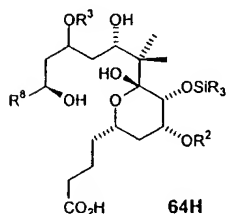
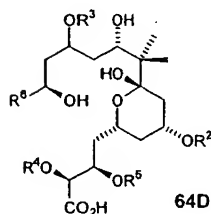
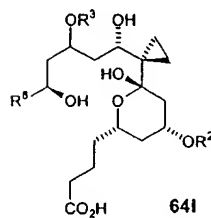
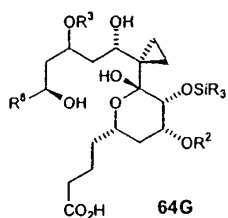
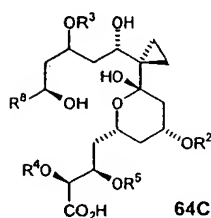
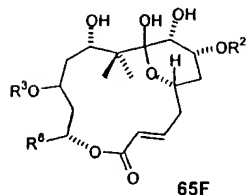
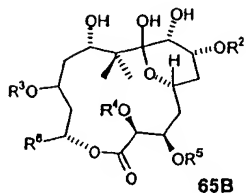
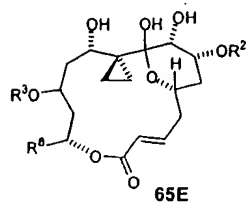
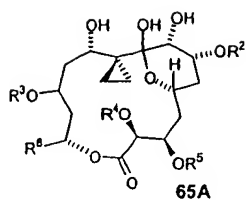


FIG. 95



R^2 , R^3 , R^4 , R^5 can be the same or different and include: H, alkyl, functionalized alkyl (functionalization may include, inter alia, heteroatoms, halides, aryl, heteroaryl), and where R^6 = aryl, heteroaryl, alkyl, functionalized alkyl, alkenyl, functionalized alkenyl, alkynyl, functionalized alkynyl (functionalization may include, inter alia, heteroatoms, halides, aryl, heteroaryl). The configuration at the carbon bearing the OR^3 substituent can have the *R*- or *S*-configuration

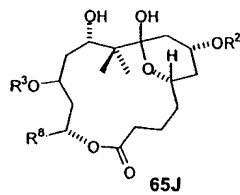
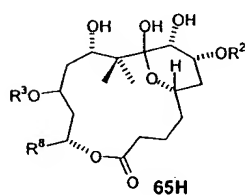
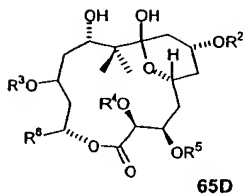
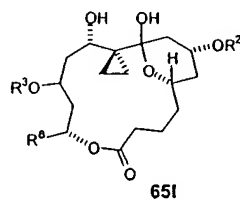
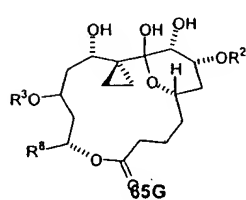
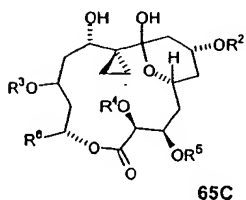


FIG. 96

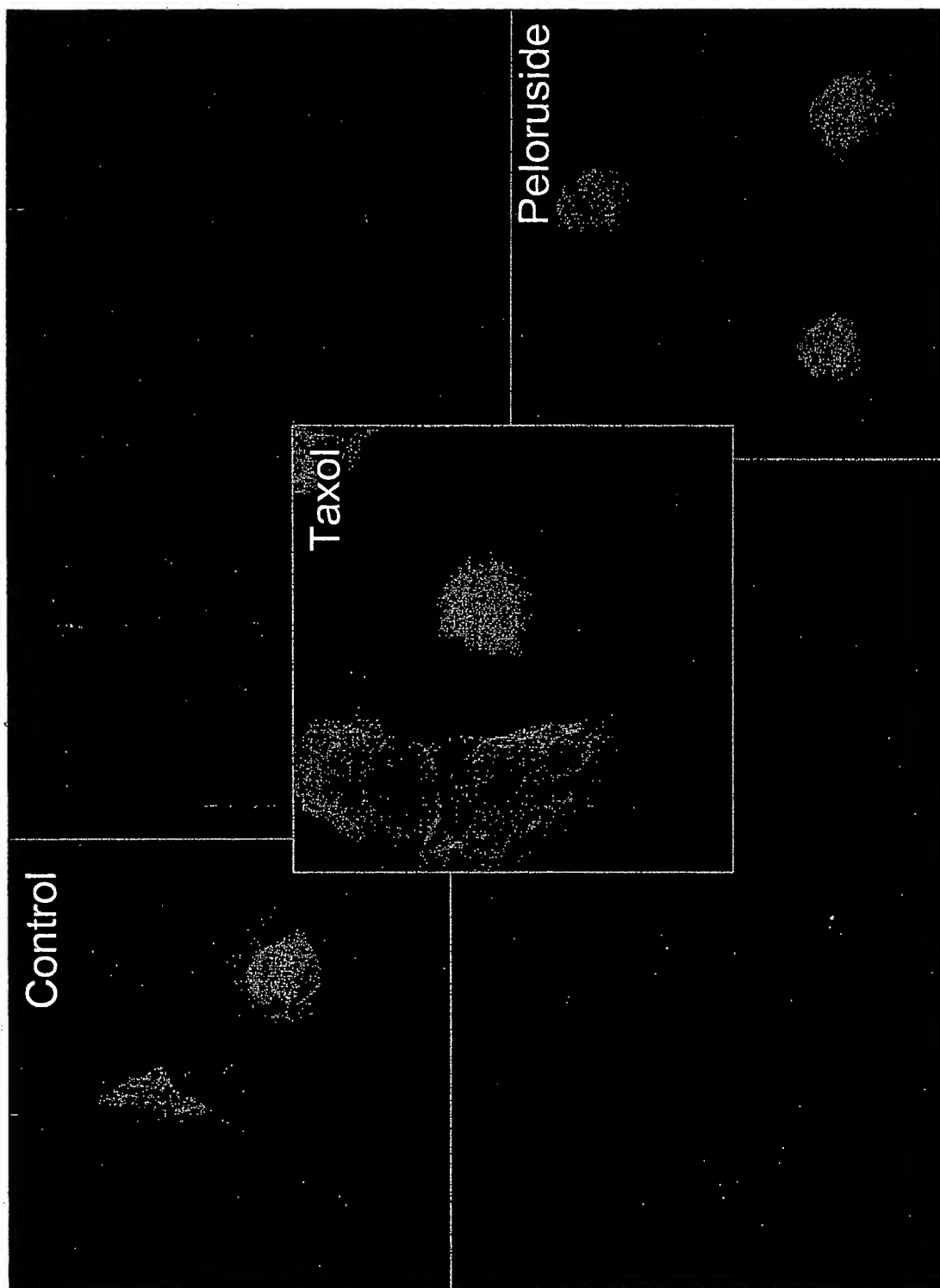


FIG. 97